IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Sitagliptin Phosphate ('708 & '921) Patent Litigation	C.A. No. 19-md-2902-RGA
MERCK SHARP & DOHME CORP., *Plaintiff*, v. AUROBINDO PHARMA LIMITED and AUROBINDO PHARMA USA, INC., *Defendants*.	C.A. No. 20-1099-RGA

FIRST AMENDED COMPLAINT

Plaintiff Merck Sharp & Dohme Corp. ("Merck"), by its attorneys, for its First Amended Complaint, alleges as follows:

1. This is an action for patent infringement under the patent laws of the United States, Title 35, United States Code, and for a declaratory judgment of patent infringement under 28 U.S.C. §§ 2201 and 2202 and the patent laws of the United States, Title 35, United States Code, that arises out of Defendants' submission of Abbreviated New Drug Application ("ANDA") No. 214859 to the U.S. Food and Drug Administration ("FDA") seeking approval to commercially manufacture, use, offer for sale, sell, and/or import versions of JANUMET® (metformin hydrochloride; sitagliptin phosphate) prior to the expiration of U.S. Patent No. 7,326,708 ("the '708 patent") and U.S. Patent No. 8,414,921 ("the '921 patent").

2. Aurobindo Pharma USA, Inc. ("Aurobindo Inc.") notified Merck by letter dated July 10, 2020 ("Aurobindo's Notice Letter") that it had submitted to the FDA ANDA No.

214859 ("Aurobindo's ANDA"), seeking approval from the FDA to engage in the commercial manufacture, use, offering for sale, sale, and/or importation of generic sitagliptin phosphate; metformin hydrochloride oral tablets ("Aurobindo's ANDA Product") prior to the expiration of the '708 patent and the '921 patent.

3. On information and belief, Aurobindo's ANDA Product is a generic version of Merck's JANUMET® product.

PARTIES

4. Plaintiff Merck is a corporation organized and existing under the laws of New Jersey, having its corporate offices and principal place of business at One Merck Drive, Whitehouse Station, New Jersey 08889.

5. Merck is the holder of New Drug Application ("NDA") No. 22044 for JANUMET® (metformin hydrochloride; sitagliptin phosphate), which has been approved by the FDA.

6. On information and belief, Defendant Aurobindo Pharma, Ltd. is a corporation organized and existing under the laws of India having its corporate offices and principal place of business at Maitri Vihar, Plot #2, Ameerpet, Hyderabad 500038, Telangana, India. On information and belief, Aurobindo Pharma, Ltd. is in the business of, among other things, manufacturing and selling generic versions of branded pharmaceutical drugs through various operating subsidiaries, including Aurobindo Pharma USA, Inc.

7. On information and belief, Defendant Aurobindo Pharma USA, Inc. is a corporation organized and existing under the laws of Delaware having its corporate offices and principal place of business at 279 Princeton-Hightstown Road, East Windsor, New Jersey 08520. On information and belief, Aurobindo Pharma USA, Inc. is in the business of, among other things,

manufacturing and selling generic versions of pharmaceutical drug products throughout the United States, including Delaware.

8. On information and belief, Aurobindo Pharma USA, Inc. is a wholly-owned subsidiary of Aurobindo Pharma, Ltd.

9. On information and belief, Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc. acted in concert to prepare and submit ANDA No. 214859 to the FDA.

10. On information and belief, Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc. know and intend that upon approval of Aurobindo's ANDA, Aurobindo Pharma, Ltd. and/or Aurobindo Pharma USA, Inc. will manufacture, market, sell, and distribute Aurobindo's ANDA Product throughout the United States, including in Delaware. On information and belief, Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc. are agents of each other and/or operate in concert as integrated parts of the same business group, including with respect to Aurobindo's ANDA Product, and enter into agreements that are nearer than arm's length. On information and belief, Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc. participated, assisted, and cooperated in carrying out the acts complained of herein. These two entities are hereafter collectively referred to as "Aurobindo."

11. On information and belief, following any FDA approval of ANDA No. 214859, Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc. will act in concert to distribute and sell Aurobindo's ANDA Product throughout the United States, including within Delaware.

JURISDICTION

12. This Court has jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

13. This Court has personal jurisdiction over Aurobindo.

14. Aurobindo Pharma, Ltd. is subject to personal jurisdiction in Delaware because, among other things, Aurobindo Pharma, Ltd., itself and through its wholly owned subsidiary Aurobindo Pharma USA, Inc., has purposefully availed itself of the benefits and protections of Delaware's laws such that it should reasonably anticipate being haled into court here. On information and belief, Aurobindo Pharma, Ltd., itself and through its wholly owned subsidiary Aurobindo Pharma USA, Inc., develops, manufactures, imports, markets, offers to sell, and/or sells generic drugs throughout the United States, including in the State of Delaware, and therefore transacts business within the State of Delaware, and/or has engaged in systematic and continuous business contacts within the State of Delaware. In addition, Aurobindo Pharma, Ltd. is subject to personal jurisdiction in Delaware because, on information and belief, it controls and dominates Aurobindo Pharma USA, Inc. and therefore the activities of Aurobindo Pharma USA, Inc. in this jurisdiction are attributed to Aurobindo Pharma, Ltd.

15. Aurobindo Pharma USA, Inc. is subject to personal jurisdiction in Delaware because, among other things, it has purposely availed itself of the benefits and protections of Delaware's laws such that it should reasonably anticipate being haled into court here. Aurobindo Pharma USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, is qualified to do business in Delaware, and has appointed a registered agent for service of process in Delaware. It therefore has consented to general jurisdiction in Delaware. In addition, on information and belief, Aurobindo Pharma USA, Inc. develops, manufactures, imports, markets, offers to sell, and/or sells generic drugs throughout the United States, including in the State of Delaware, and therefore transacts business within the State of Delaware related to Merck's claims, and/or has engaged in systematic and continuous business contacts within the State of Delaware.

16. On information and belief, if Aurobindo's ANDA is approved, Aurobindo will manufacture, market, sell, and/or distribute Aurobindo's ANDA Product within the United States, including in Delaware, consistent with Aurobindo's practices for the marketing and distribution of other generic pharmaceutical products. On information and belief, Aurobindo regularly does business in Delaware, and its practices with other generic pharmaceutical products have involved placing those products into the stream of commerce for distribution throughout the United States, including in Delaware. On information and belief, Aurobindo's generic pharmaceutical products are used and/or consumed within and throughout the United States, including in Delaware. On information and belief, Aurobindo's ANDA Product will be prescribed by physicians practicing in Delaware, dispensed by pharmacies located within Delaware, and used by patients in Delaware. Each of these activities would have a substantial effect within Delaware and would constitute infringement of Merck's patent in the event that Aurobindo's ANDA Product is approved before the '708 patent or the '921 patent expires.

17. On information and belief, Aurobindo derives substantial revenue from generic pharmaceutical products that are used and/or consumed within Delaware, and that are manufactured by Aurobindo and/or for which Aurobindo Pharma, Ltd. and/or Aurobindo Pharma USA, Inc. is/are the named applicant(s) on approved ANDAs. On information and belief, various products for which Aurobindo Pharma, Ltd. and/or Aurobindo Pharma USA, Inc. is/are the named applicant(s) on approved ANDAs are available at retail pharmacies in Delaware.

18. In addition, this Court has personal jurisdiction over Aurobindo because Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc. regularly engage in patent litigation concerning FDA-approved branded drug products in this district, do not contest personal jurisdiction in this district, and have purposefully availed themselves of the rights and benefits of

this Court by asserting claims and/or counterclaims in this Court. *See Merck Sharp & Dohme Corp. v. Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc.*, Case No. 20-949-RGA (D. Del. July 15, 2020) (Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc.); *see also Pfizer Inc. v. Aziant Drug Research Sols. Pvt. Ltd.*, C.A. No. 19-743-CFC (D. Del. Apr. 7, 2020) (Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc.); *Taiho Pharm. Co. v. Eugia Pharma Specialities Ltd.*, C.A. No. 19-2309-CFC (D. Del. Mar. 23, 2020) (Aurobindo Pharma USA, Inc.); *Millennium Pharm. v. Aurobindo Pharma USA, Inc.*, C.A. No. 19-471-CFC (D. Del. Dec. 26, 2019) (Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc.); *Pfizer Inc. v. Aurobindo Pharma, Ltd.*, C.A. No. 19-748-CFC (D. Del. July 8, 2019) (Aurobindo Pharma, Ltd. and Aurobindo Pharma USA, Inc.).

THE '708 PATENT

19. Merck incorporates each of the preceding paragraphs 1–18 as if fully set forth herein.

20. The inventors named on the '708 patent are Stephen Howard Cypes, Alex Minhua Chen, Russell R. Ferlita, Karl Hansen, Ivan Lee, Vicky K. Vydra, and Robert M. Wenslow, Jr.

21. The '708 patent, entitled "Phosphoric Acid Salt of a Dipeptidyl Peptidase-IV Inhibitor" (attached as Exhibit A), was duly and legally issued on February 5, 2008.

22. Merck is the owner and assignee of the '708 patent.

23. The '708 patent claims, *inter alia*, a dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I, or a hydrate thereof, as recited in claim 1 of the '708 patent.

24. JANUMET®, as well as methods of using JANUMET®, are covered by one or more claims of the '708 patent, including claim 1 of the '708 patent, and the '708 patent has been listed in connection with JANUMET® in the FDA's Orange Book.

THE '921 PATENT

25. Merck incorporates each of the preceding paragraphs 1–24 as if fully set forth herein.

26. The inventors named on the '921 patent are Ashkan Kamali, Laman Alani, Kyle Fliszar, Soumojeet Ghosh, and Monica Tijerina.

27. The '921 patent, entitled "Pharmaceutical Compositions of Combinations of Dipeptidyl Peptidase-4 Inhibitors with Metformin" (attached as Exhibit B), was duly and legally issued on April 9, 2013.

28. Merck is the owner and assignee of the '921 patent.

29. The '921 patent claims, inter alia, a pharmaceutical composition comprising: (a) about 3 to 20% by weight of sitagliptin, or a pharmaceutically acceptable salt thereof; (b) about 25 to 94% by weight of metformin hydrochloride; (c) about 0.1 to 10% by weight of a lubricant; (d) about 0 to 35% by weight of a binding agent; (e) about 0.5 to 1% by weight of a surfactant; and (f) about 5 to 15% by weight of a diluent, as recited in claim 1 of the '921 patent.

30. JANUMET®, as well as methods of using JANUMET®, are covered by one or more claims of the '921 patent, including claim 1 of the '921 patent, and the '921 patent has been listed in connection with JANUMET® in the FDA's Orange Book.

COUNT I – INFRINGEMENT OF THE '708 PATENT

31. Merck incorporates each of the preceding paragraphs 1–30 as if fully set forth herein.

32. In Aurobindo's Notice Letter, Aurobindo notified Merck of the submission of Aurobindo's ANDA to the FDA. The purpose of this submission was to obtain approval under the FDCA to engage in the commercial manufacture, use, offer for sale, sale and/or importation of Aurobindo's ANDA Product prior to the expiration of the '708 patent.

33. In Aurobindo's Notice Letter, Aurobindo also notified Merck that, as part of its ANDA, Aurobindo had filed certifications of the type described in Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355 (j)(2)(A)(vii)(IV), with respect to the '708 patent. On information and belief, Aurobindo submitted its ANDA to the FDA containing certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the '708 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, offer for sale, sale, and/or importation of Aurobindo's ANDA Product.

34. In Aurobindo's Notice Letter, Aurobindo stated that Aurobindo's ANDA Product contains sitagliptin phosphate as an active ingredient.

35. Aurobindo's ANDA Product, and the use of Aurobindo's ANDA Product, is covered by one or more claims of the '708 patent, including at least claim 1 of the '708 patent, because claim 1 of the '708 patent covers the sitagliptin phosphate contained in Aurobindo's ANDA Product.

36. In Aurobindo's Notice Letter, Aurobindo did not contest infringement of claim 1 of the '708 patent.

37. Aurobindo's submission of Aurobindo's ANDA for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Aurobindo's ANDA Product before the expiration of the '708 patent was an act of infringement of the '708 patent under 35 U.S.C. § 271(e)(2)(A).

38. On information and belief, Aurobindo will engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Aurobindo's ANDA Product immediately and imminently upon approval of its ANDA.

39. The manufacture, use, sale, offer for sale, or importation of Aurobindo's ANDA Product would infringe one or more claims of the '708 patent, including at least claim 1 of the '708 patent.

40. On information and belief, the manufacture, use, sale, offer for sale, or importation of Aurobindo's ANDA Product in accordance with, and as directed by, its proposed product labeling would infringe one or more claims of the '708 patent, including at least claim 1 of the '708 patent.

41. On information and belief, Aurobindo plans and intends to, and will, actively induce infringement of the '708 patent when Aurobindo's ANDA is approved, and plans and intends to, and will, do so immediately and imminently upon approval. Aurobindo's activities will be done with knowledge of the '708 patent and specific intent to infringe that patent.

42. On information and belief, Aurobindo knows that Aurobindo's ANDA Product and its proposed labeling are especially made or adapted for use in infringing the '708 patent, that Aurobindo's ANDA Product is not a staple article or commodity of commerce, and that Aurobindo's ANDA Product and its proposed labeling are not suitable for substantial noninfringing use. On information and belief, Aurobindo plans and intends to, and will, contribute to infringement of the '708 patent immediately and imminently upon approval of Aurobindo's ANDA.

43. Notwithstanding Aurobindo's knowledge of the claims of the '708 patent, Aurobindo has continued to assert its intent to manufacture, offer for sale, sell, distribute, and/or

import Aurobindo's ANDA Product with its product labeling following FDA approval of Aurobindo's ANDA prior to the expiration of the '708 patent.

44. The foregoing actions by Aurobindo constitute and/or will constitute infringement of the '708 patent; active inducement of infringement of the '708 patent; and contribution to the infringement by others of the '708 patent.

45. On information and belief, Aurobindo has acted with full knowledge of the '708 patent and without a reasonable basis for believing that it would not be liable for infringement of the '708 patent; active inducement of infringement of the '708 patent; and/or contribution to the infringement by others of the '708 patent.

46. Merck will be substantially and irreparably damaged by infringement of the '708 patent.

47. Unless Aurobindo is enjoined from infringing the '708 patent, actively inducing infringement of the '708 patent, and contributing to the infringement by others of the '708 patent, Merck will suffer irreparable injury. Merck has no adequate remedy at law.

COUNT II – DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '708 PATENT

48. Merck incorporates each of the preceding paragraphs 1–47 as if fully set forth herein.

49. The Court may declare the rights and legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because there is a case of actual controversy between Merck on the one hand and Aurobindo on the other regarding Aurobindo's infringement, active inducement of infringement, and contribution to the infringement by others of the '708 patent.

50. The Court should declare that the commercial manufacture, use, sale, offer for sale or importation of Aurobindo's ANDA Product with its proposed labeling, or any other

Aurobindo drug product that is covered by or whose use is covered by the '708 patent, will infringe, induce the infringement of, and contribute to the infringement by others of the '708 patent, and that the claims of the '708 patent are valid.

COUNT III – INFRINGEMENT OF THE '921 PATENT

51. Merck incorporates each of the preceding paragraphs 1–50 as if fully set forth herein.

52. In Aurobindo's Notice Letter, Aurobindo notified Merck of the submission of Aurobindo's ANDA Product to the FDA. The purpose of this submission was to obtain approval under the FDCA to engage in the commercial manufacture, use, offer for sale, sale and/or importation of Aurobindo's ANDA Product prior to the expiration of the '921 patent.

53. In Aurobindo's Notice Letter, Aurobindo also notified Merck that, as part of its ANDA, Aurobindo had filed certifications of the type described in Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355 (j)(2)(A)(vii)(IV), with respect to the '921 patent. On information and belief, Aurobindo submitted its ANDA to the FDA containing certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the '921 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, offer for sale, sale, and/or importation of Aurobindo's ANDA Product.

54. Aurobindo's ANDA Product, and the use of Aurobindo's ANDA Product, are covered by one or more claims of the '921 patent, including at least claim 1 of the '921 patent, because the composition of Aurobindo's ANDA Product includes the same or equivalent ingredients as recited in claim 1 of the '921 patent in the same or equivalent amounts.

55. Aurobindo's submission of Aurobindo's ANDA for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale, and/or

importation of Aurobindo's ANDA Product before the expiration of the '921 patent was an act of infringement of the '921 patent under 35 U.S.C. § 271(e)(2)(A).

56. On information and belief, Aurobindo will engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Aurobindo's ANDA Product immediately and imminently upon approval of its ANDA.

57. The manufacture, use, sale, offer for sale, or importation of Aurobindo's ANDA Product would infringe one or more claims of the '921 patent, including at least claim 1 of the '921 patent.

58. On information and belief, the manufacture, use, sale, offer for sale, or importation of Aurobindo's ANDA Product in accordance with, and as directed by, its proposed product labeling would infringe one or more claims of the '921 patent, including at least claim 1 of the '921 patent.

59. On information and belief, Aurobindo plans and intends to, and will, actively induce infringement of the '921 patent when Aurobindo's ANDA is approved, and plans and intends to, and will, do so immediately and imminently upon approval. Aurobindo's activities will be done with knowledge of the '921 patent and specific intent to infringe that patent.

60. On information and belief, Aurobindo knows that Aurobindo's ANDA Product and its proposed labeling are especially made or adapted for use in infringing the '921 patent, that Aurobindo's ANDA Product is not a staple article or commodity of commerce, and that Aurobindo's ANDA Product and its proposed labeling are not suitable for substantial noninfringing use.

61. On information and belief, Aurobindo plans and intends to, and will, contribute to infringement of the ’921 patent immediately and imminently upon approval of Aurobindo’s ANDA.

62. Notwithstanding Aurobindo’s knowledge of the claims of the ’921 patent, Aurobindo has continued to assert its intent to manufacture, offer for sale, sell, distribute, and/or import Aurobindo’s ANDA Product with its product labeling following FDA approval of Aurobindo’s ANDA prior to the expiration of the ’921 patent.

63. The foregoing actions by Aurobindo constitute and/or will constitute infringement of the ’921 patent; active inducement of infringement of the ’921 patent; and contribution to the infringement by others of the ’921 patent.

64. On information and belief, Aurobindo has acted with full knowledge of the ’921 patent and without a reasonable basis for believing that it would not be liable for infringement of the ’921 patent; active inducement of infringement of the ’921 patent; and/or contribution to the infringement by others of the ’921 patent.

65. Merck will be substantially and irreparably damaged by infringement of the ’921 patent.

66. Unless Aurobindo is enjoined from infringing the ’921 patent, actively inducing infringement of the ’921 patent, and contributing to the infringement by others of the ’921 patent, Merck will suffer irreparable injury. Merck has no adequate remedy at law.

COUNT IV – DECLARATORY JUDGMENT OF INFRINGEMENT OF THE ’921 PATENT

67. Merck incorporates each of the preceding paragraphs 1–66 as if fully set forth herein.

68. The Court may declare the rights and legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because there is a case of actual controversy between Merck on the one hand and Aurobindo on the other regarding Aurobindo's infringement, active inducement of infringement, and contribution to the infringement by others of the '921 patent.

69. The Court should declare that the commercial manufacture, use, sale, offer for sale or importation of Aurobindo's ANDA Product with its proposed labeling, or any other Aurobindo drug product that is covered by or whose use is covered by the '921 patent, will infringe, induce the infringement of, and contribute to the infringement by others of the '921 patent, and that the claims of the '921 patent are valid..

PRAYER FOR RELIEF

WHEREFORE, Merck requests the following relief:

(a) A judgment that the '708 patent has been infringed under 35 U.S.C. § 271(e)(2) by Aurobindo's submission to the FDA of Aurobindo's ANDA;

(b) A judgment ordering that the effective date of any FDA approval of the commercial manufacture, use, or sale of Aurobindo's ANDA Product, or any other drug product that infringes or the use of which infringes the '708 patent, be not earlier than the latest of the expiration date of the '708 patent, inclusive of any extension(s) and additional period(s) of exclusivity;

(c) A preliminary and permanent injunction enjoining Aurobindo, and all persons acting in concert with Aurobindo, from the commercial manufacture, use, sale, offer for sale, or importation into the United States of Aurobindo's ANDA Product, or any other drug product covered by or whose use is covered by the '708 patent, prior to the expiration of the '708 patent, inclusive of any extension(s) and additional period(s) of exclusivity;

(d) A judgment declaring that the commercial manufacture, use, sale, offer for sale or importation of Aurobindo's ANDA Product, or any other drug product that is covered by or whose use is covered by the '708 patent, prior to the expiration of the '708 patent, will infringe, induce the infringement of, and contribute to the infringement by others of, the '708 patent;

(e) A judgment that the '921 patent has been infringed under 35 U.S.C. § 271(e)(2) by Aurobindo's submission to the FDA of Aurobindo's ANDA;

(f) A judgment ordering that the effective date of any FDA approval of the commercial manufacture, use, or sale of Aurobindo's ANDA Product, or any other drug product that infringes or the use of which infringes the '921 patent, be not earlier than the latest of the expiration date of the '921 patent, inclusive of any extension(s) and additional period(s) of exclusivity;

(g) A preliminary and permanent injunction enjoining Aurobindo, and all persons acting in concert with Aurobindo, from the commercial manufacture, use, sale, offer for sale, or importation into the United States of Aurobindo's ANDA Product, or any other drug product covered by or whose use is covered by the '921 patent, prior to the expiration of the '921 patent, inclusive of any extension(s) and additional period(s) of exclusivity;

(h) A judgment declaring that the commercial manufacture, use, sale, offer for sale or importation of Aurobindo's ANDA Product, or any other drug product that is covered by or whose use is covered by the '921 patent, prior to the expiration of the '921 patent, will infringe, induce the infringement of, and contribute to the infringement by others of, the '921 patent;

(i) A declaration that this is an exceptional case and an award of attorney's fees pursuant to 35 U.S.C. § 285;

(j) Costs and expenses in this action; and

(k) Such further and other relief as this Court may deem just and proper.

Dated: February 16, 2021

Respectfully submitted,

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**Admitted only in Michigan. Practice supervised by D.C. Bar members pursuant to D.C. Court of Appeals Rule 49(c)(8).*

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EXHIBIT A

US007326708B2

(12) **United States Patent**
Cypes et al.

(10) **Patent No.: US 7,326,708 B2**
(45) **Date of Patent: Feb. 5, 2008**

(54) **PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR**

(75) Inventors: **Stephen Howard Cypes**, Santa Clara, CA (US); **Alex Minhua Chen**, Metuchen, NJ (US); **Russell R. Ferlita**, Westfield, NJ (US); **Karl Hansen**, Atlantic Highlands, NJ (US); **Ivan Lee**, Piscataway, NJ (US); **Vicky K. Vydra**, Fair Lawn, NJ (US); **Robert M. Wenslow, Jr.**, East Windsor, NJ (US)

(73) Assignee: **Merck & Co., Inc.**, Rahway, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 657 days.

(21) Appl. No.: **10/874,992**

(22) Filed: **Jun. 23, 2004**

(65) **Prior Publication Data**

US 2005/0032804 A1 Feb. 10, 2005

Related U.S. Application Data

(60) Provisional application No. 60/482,161, filed on Jun. 24, 2003.

(51) **Int. Cl.**
A61K 31/495 (2006.01)
C07D 471/04 (2006.01)

(52) **U.S. Cl.** **514/249**; 544/350

(58) **Field of Classification Search** 514/249; 544/350

See application file for complete search history.

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(57) **ABSTRACT**

The dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine is a potent inhibitor of dipeptidyl peptidase-IV and is useful for the prevention and/or treatment of non-insulin dependent diabetes mellitus, also referred to as type 2 diabetes. The invention also relates to a crystalline monohydrate of the dihydrogenphosphate salt as well as a process for its preparation, pharmaceutical compositions containing this novel form and methods of use for the treatment of diabetes, obesity, and high blood pressure.

24 Claims, 5 Drawing Sheets

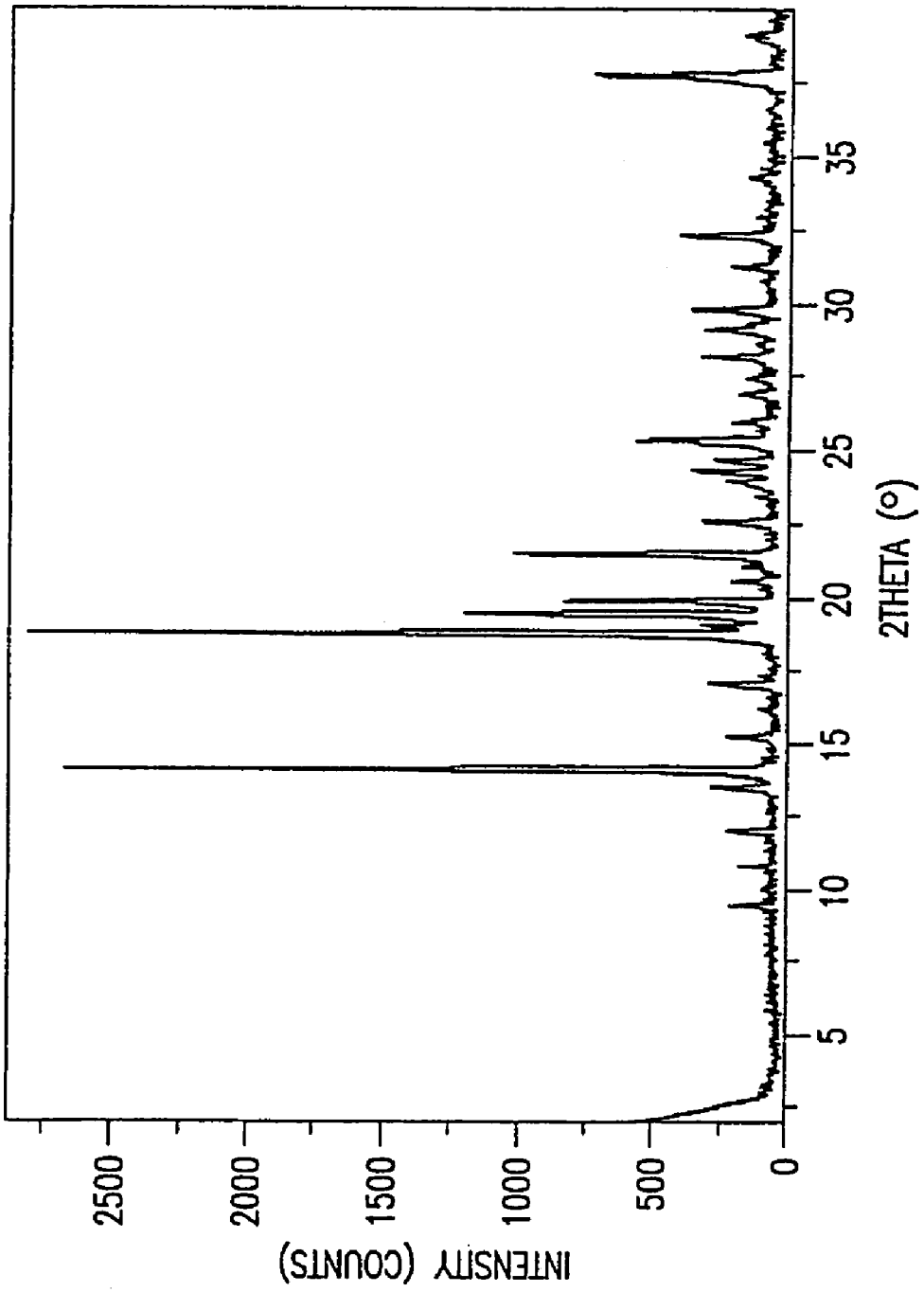

INTENSITY (COUNTS)
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2THETA (°)

FIG. 1

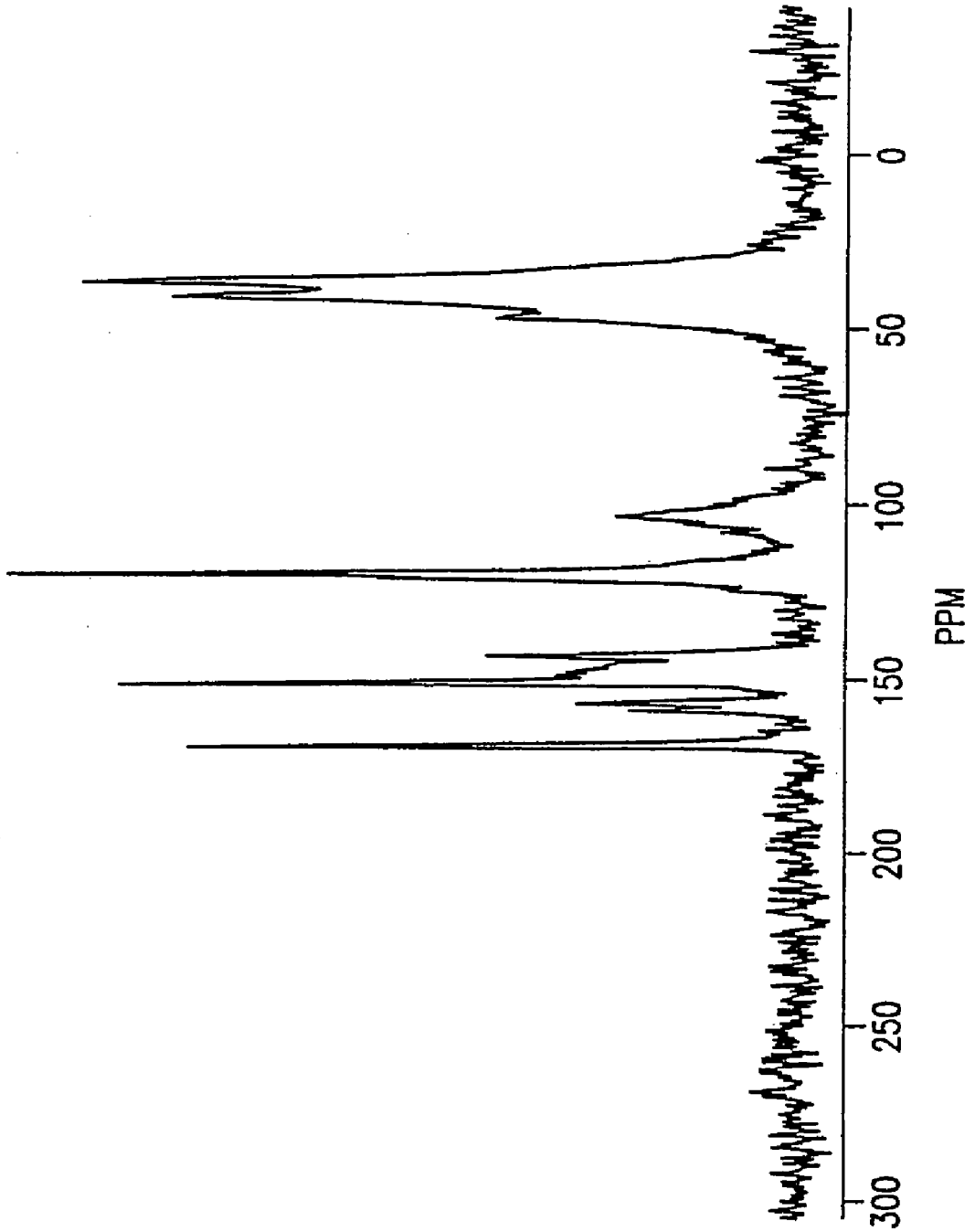


FIG. 2

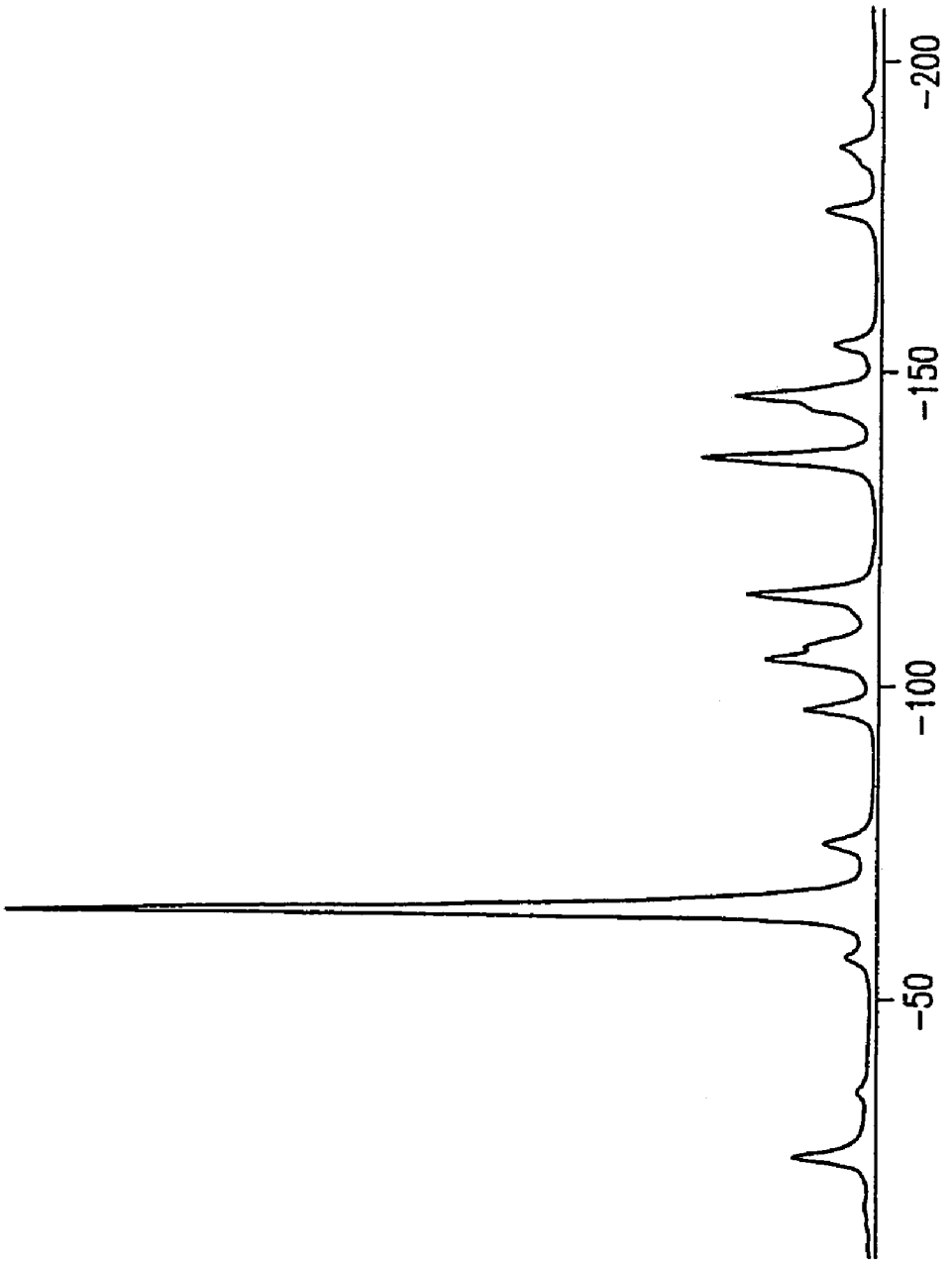


FIG. 3

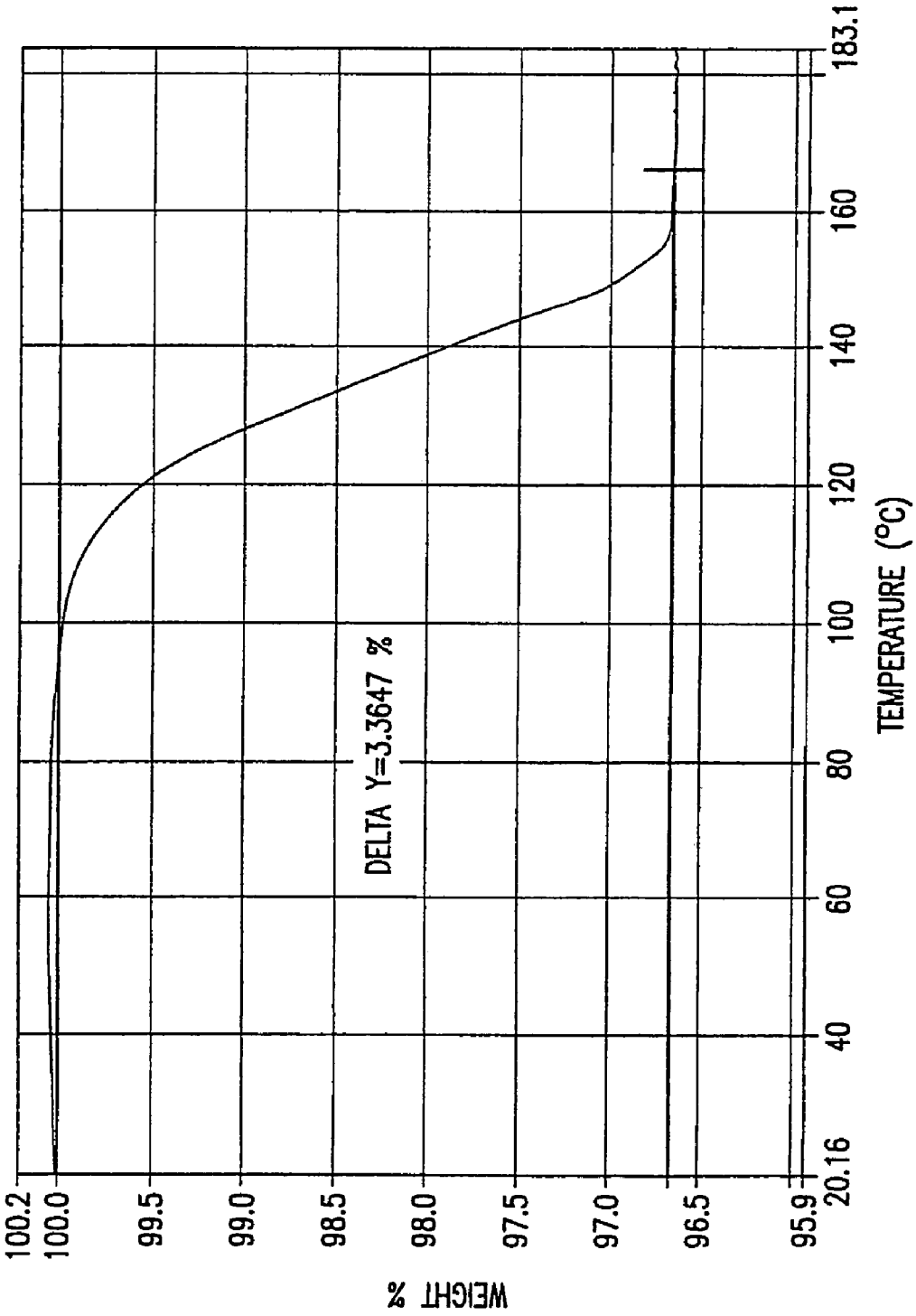

DELTA Y=3.3647 %
WEIGHT %
100.2
100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
95.9
TEMPERATURE (°C)
20.16
40
60
80
100
120
140
160
183.1

FIG. 4

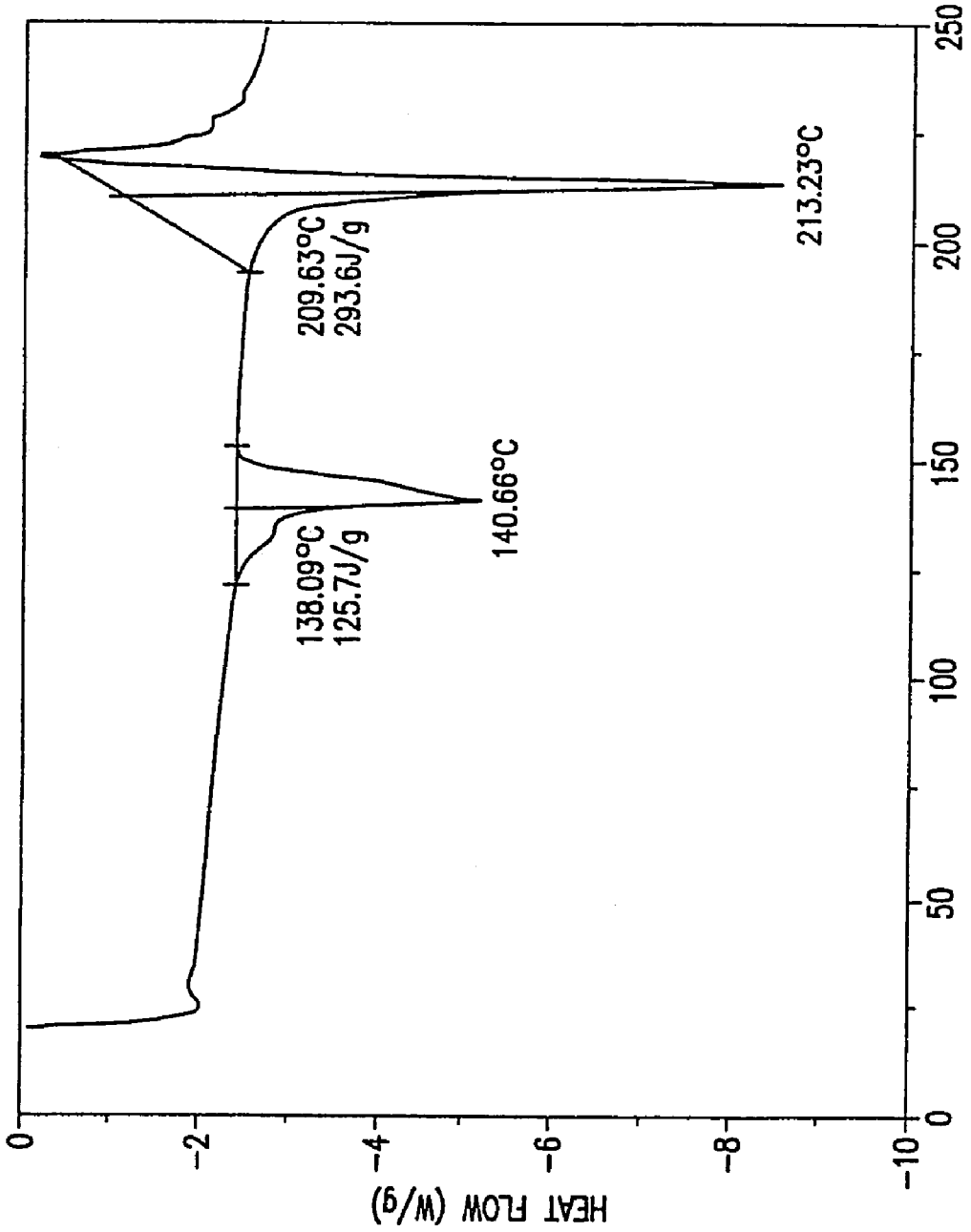

213.23°C
209.63°C
293.6J/g
140.66°C
138.09°C
125.7J/g
HEAT FLOW (W/g)
TEMPERATURE (°C)
0
-2
-4
-6
-8
-10
0
50
100
150
200
250

FIG.5

PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATIONS

The present invention is related to U.S. provisional application Ser. No. 60/482,161, filed Jun. 24, 2003, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to a particular salt of a dipeptidyl peptidase-IV inhibitor. More particularly, the invention relates to a dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, which is a potent inhibitor of dipeptidyl peptidase-IV. This novel salt and crystalline hydrates thereof are useful for the treatment and prevention of diseases and conditions for which an inhibitor of dipeptidyl peptidase-IV is indicated, in particular Type 2 diabetes, obesity, and high blood pressure. The invention further concerns pharmaceutical compositions comprising the dihydrogenphosphate salt and crystalline hydrates thereof useful to treat Type 2 diabetes, obesity, and high blood pressure as well as processes for preparing the dihydrogenphosphate salt and crystalline hydrates thereof and their pharmaceutical compositions.

BACKGROUND OF THE INVENTION

Inhibition of dipeptidyl peptidase-IV (DP-IV), an enzyme that inactivates both glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), represents a novel approach to the treatment and prevention of Type 2 diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM). The therapeutic potential of DP-IV inhibitors for the treatment of Type 2 diabetes has been reviewed: C. F. Deacon and J. J. Holst, "Dipeptidyl peptidase IV inhibition as an approach to the treatment and prevention of Type 2 diabetes: a historical perspective," *Biochem. Biophys. Res. Commun.,* 294: 1-4 (2000); K. Augustyns, et al., "Dipeptidyl peptidase IV inhibitors as new therapeutic agents for the treatment of Type 2 diabetes," *Expert. Opin. Ther. Patents,* 13: 499-510 (2003); and D. J. Drucker, "Therapeutic potential of dipeptidyl peptidase IV inhibitors for the treatment of Type 2 diabetes," *Expert Opin. Investig. Drugs,* 12: 87-100 (2003).

WO 03/004498 (published 16 Jan. 2003), assigned to Merck & Co., describes a class of beta-amino tetrahydrotriazolo[4,3-a]pyrazines, which are potent inhibitors of DP-IV and therefore useful for the treatment of Type 2 diabetes. Specifically disclosed in WO 03/004498 is 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine. Pharmaceutically acceptable salts of this compound are generically encompassed within the scope of WO 03/004498.

However, there is no specific disclosure in the above reference of the newly discovered monobasic dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I below.

SUMMARY OF THE INVENTION

The present invention is concerned with a novel dihydrogenphosphate salt of the dipeptidyl peptidase-IV (DP-IV) inhibitor 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine and crystalline hydrates thereof, in particular a crystalline monohydrate. The dihydrogenphosphate salt and crystalline hydrates of the present invention have advantages in the preparation of pharmaceutical compositions of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, such as ease of processing, handling, and dosing. In particular, they exhibit improved physical and chemical stability, such as stability to stress, high temperatures and humidity, as well as improved physicochemical properties, such as solubility and rate of solution, rendering them particularly suitable for the manufacture of various pharmaceutical dosage forms. The invention also concerns pharmaceutical compositions containing the novel salt and hydrates as well as methods for using them as DP-IV inhibitors, in particular for the prevention or treatment of Type 2 diabetes, obesity, and high blood pressure.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a characteristic X-ray diffraction pattern of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

FIG. **2** is a carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) spectrum of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

FIG. **3** is a fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance (NMR) spectrum of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

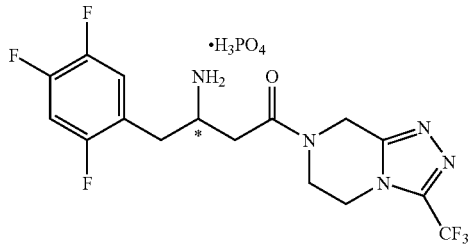
FIG. **4** is a typical thermogravimetric analysis (TGA) curve of the crystalline monohydrate dihydrogenphosphate salt of structural formula II.

FIG. **5** is a typical differential scanning calorimetry (DSC) curve of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a new monobasic dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1 ,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine of the following structural formula I:

(I)



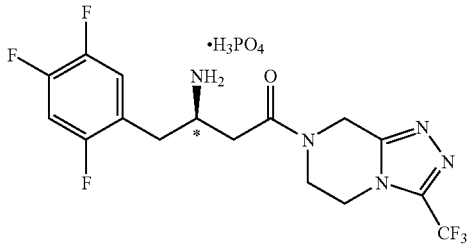
or a crystalline hydrate thereof. In particular, the instant invention provides a crystalline monohydrate of the dihydrogenphosphate salt of formula I.

The dihydrogenphosphate salt of the present invention has a center of asymmetry at the stereogenic carbon atom

indicated with an * and can thus occur as a racemate, racemic mixture, and single enantiomers, with all isomeric forms being included in the present invention. The separate enantiomers, substantially free of the other, are included within the scope of the invention, as well as mixtures of the two enantiomers.

One embodiment of the present invention provides the dihydrogenphosphate salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-triflorophenyl) butan-2-amine of structural formula II:

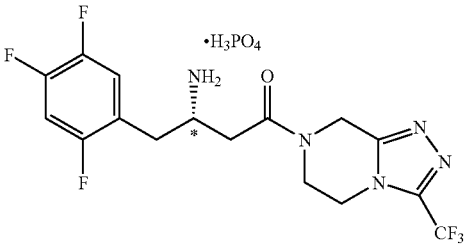
(II)



or a crystalline hydrate thereof.

A second embodiment of the present invention provides the dihydrogenphosphate salt of (2S)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine of structural formula III:

(III)



or a crystalline hydrate thereof.

More specifically, the dihydrogenphosphate salt of the present invention is comprised of one molar equivalent of mono-protonated 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine cation and one molar equivalent of dihydrogenphosphate (biphosphate) anion.

In a further embodiment of the present invention, the dihydrogenphosphate salt of structural formulae I-III is a crystalline hydrate. In one class of this embodiment, the crystalline hydrate is a crystalline monohydrate.

A further embodiment of the present invention provides the dihydrogenphosphate salt drug substance of structural formulae I-III that comprises the crystalline monohydrate present in a detectable amount. By "drug substance" is meant the active pharmaceutical ingredient ("API"). The amount of crystalline monohydrate in the drug substance can be quantified by the use of physical methods such as X-ray powder diffraction, solid-state fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance spectroscopy, solid-state carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance spectroscopy, solid state Fourier-transform infrared spectroscopy, and Raman spectroscopy. In a class of this embodiment, about 5% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a second class of this embodiment, about 10% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a third class of this embodiment, about 25% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a fourth class of this embodiment, about 50% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a fifth class of this embodiment, about 75% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a sixth class of this embodiment, substantially all of the dihydrogenphosphate salt drug substance is the crystalline monohydrate of the present invention, i.e., the dihydrogenphosphate salt drug substance is substantially phase pure monohydrate.

The crystalline dihydrogenphosphate salt of the present invention exhibits pharmaceutic advantages over the free base and the previously disclosed hydrochloride salt (WO 03/004498) in the preparation of a pharmaceutical drug product containing the pharmacologically active ingredient. In particular, the enhanced chemical and physical stability of the crystalline dihydrogenphosphate salt monohydrate constitute advantageous properties in the preparation of solid pharmaceutical dosage forms containing the pharmacologically active ingredient.

The dihydrogenphosphate salt of the present invention, which exhibits potent DP-IV inhibitory properties, is particularly useful for the prevention or treatment of Type 2 diabetes, obesity, and high blood pressure.

Another aspect of the present invention provides a method for the prevention or treatment of clinical conditions for which an inhibitor of DP-IV is indicated, which method comprises administering to a patient in need of such prevention or treatment a prophylactically or therapeutically effective amount of the dihydrogenphosphate salt of structural formula I or a hydrate thereof, in particular the crystalline monohydrate thereof. Such clinical conditions include diabetes, in particular Type 2 diabetes, hyperglycemia, insulin resistance, and obesity.

The present invention also provides the use of the dihydrogenphosphate salt of structural formula I or a hydrate thereof, in particular the crystalline monohydrate, for the manufacture of a medicament for the prevention or treatment of clinical conditions for which an inhibitor of DP-IV is indicated.

The present invention also provides pharmaceutical compositions comprising the dihydrogenphosphate salt of structural formula I or a hydrate thereof, in particular the crystalline monohydrate, in association with one or more pharmaceutically acceptable carriers or excipients. In one embodiment the pharmaceutical composition comprise a therapeutically effective amount of the active pharmaceutical ingredient in admixture with pharmaceutically acceptable excipients wherein the active pharmaceutical ingredient comprises a detectable amount of the crystalline monohydrate of the present invention. In a second embodiment the pharmaceutical composition comprise a therapeutically effective amount of the active pharmaceutical ingredient in admixture with pharmaceutically acceptable excipients wherein the active pharmaceutical ingredient comprises about 5% to about 100% by weight of the crystalline monohydrate of the present invention. In a class of this second embodiment, the active pharmaceutical ingredient in such compositions comprises about 10% to about 100% by

weight of the crystalline monohydrate. In a second class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 25% to about 100% by weight of the crystalline monohydrate. In a third class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 50% to about 100% by weight of the crystalline monohydrate. In a fourth class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 75% to about 100% by weight of the crystalline monohydrate. In a fifth class of this embodiment, substantially all of the active pharmaceutical ingredient is the crystalline dihydrogenphosphate salt monohydrate of the present invention, i.e., the active pharmaceutical ingredient is substantially phase pure dihydrogenphosphate salt monohydrate.

The compositions in accordance with the invention are suitably in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories. The compositions are intended for oral, parenteral, intranasal, sublingual, or rectal administration, or for administration by inhalation or insufflation. Formulation of the compositions according to the invention can conveniently be effected by methods known from the art, for example, as described in *Remington's Pharmaceutical Sciences,* 17th ed., 1995.

The dosage regimen is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; and the renal and hepatic function of the patient. An ordinarily skilled physician, veterinarian, or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 200, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 200 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, the crystalline forms of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, the crystalline forms of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

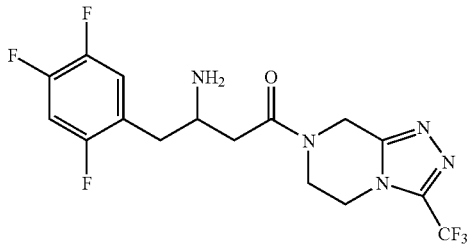
In the methods of the present invention, the dihydrogenphosphate salt and crystalline hydrates herein described in detail can form the active pharmaceutical ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active pharmaceutical ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the active pharmaceutical ingredient can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The dihydrogenphosphate salt of structural formula I and the crystalline monohydrate have been found to possess a high solubility in water, rendering it especially amenable to the preparation of formulations, in particular intranasal and intravenous formulations, which require relatively concentrated aqueous solutions of active ingredient. The solubility of the crystalline dihydrogenphosphate salt monohydrate of formula I in water has been found to be about 72 mg/mL.

According to a further aspect, the present invention provides a process for the preparation of the dihydrogenphosphate salt of formula I, which process comprises reacting 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluoromethyl)butan-2-amine of structural formula IV below:

(IV)



with approximately one equivalent of phosphoric acid in a suitable C_1-C_5 alkanol, such as methanol, ethanol, isopropyl alcohol (IPA), and isoamyl alcohol (IAA) or aqueous C_1-C_5 alkanol. The reaction is carried out at a temperature range of about 25 ° C. to about 80 ° C. The phosphoric acid solution can be added to a solution of the amine, or the addition can be performed in the reverse direction. The crystalline dihydrogenphosphate salt monohydrate is obtained by crystallization from an aqueous C_1-C_5 alkanol solution of the dihydrogenphosphate salt as described below.

General Methods for Crystallizing the Monohydrate of the Dihydrogenphosphate Salt of Structural Formula I

(a) In Ethanol/Water System at 25° C.:

(1) crystallization from a mixture of compound I in ethanol and water, such that the water concentration is above 31 weight percent,

(2) recovering the resultant solid phase, and

(3) removing the solvent therefrom.

(b) In Isoamyl Alcohol (IAA)/Water System at 25° C.:

(1) crystallization from a mixture of compound I in IAA and water, such that the water concentration is above 2.9 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom.

(c) In IAA/Water System at 40° C.:

(1) crystallization from a mixture of compound I in IAA and water, such that the water concentration is above 3.6 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom

(d) In IAA/Water System at 60° C.:

(1) crystallization from a mixture of compound I in IAA and water, such that the water concentration is above 4.5 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom.

(e) In Isopropyl Alcohol (IPA)/Water System at 25° C.:

(1) crystallization from a mixture of compound I in IPA and water, such that the water concentration is above 7.0 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom

(f) In IPA/Water System at 40° C.:

(1) crystallization from a mixture of compound I in EPA and water, such that the water concentration is above 8.1 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom.

(g) In IPA/Water System at 75° C.:

(1) crystallization from a mixture of compound I in IPA and water, such that the water concentration is above about 20 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom.

The starting compound of structural formula IV can be prepared by the procedures detailed in Schemes 1-3 and Example 1 below.

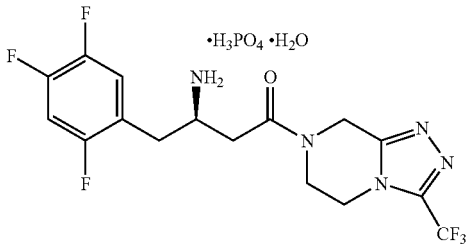
In a still further aspect, the present invention provides a method for the treatment and/or prevention of clinical conditions for which a DP-IV inhibitor is indicated, which method comprises administering to a patient in need of such prevention or treatment a prophylactically or therapeutically effective amount of the salt of Formula I as defined above or a crystalline hydrate thereof.

The following non-limiting Examples are intended to illustrate the present invention and should not be construed as being limitations on the scope or spirit of the instant invention.

Compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of structural formula I.

The term "% enantiomeric excess" (abbreviated "ee") shall mean the % major enantiomer less the % minor enantiomer. Thus, a 70% enantiomeric excess corresponds to formation of 85% of one enantiomer and 15% of the other. The term "enantiomeric excess" is synonymous with the term "optical purity."

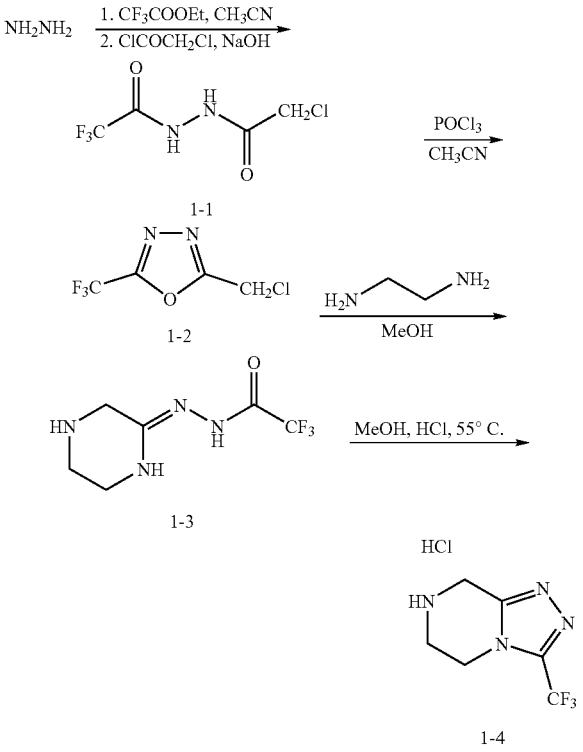
EXAMPLE



(2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine dihydrogenphosphate monohydrate

Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,41]triazolo[4,3-a]pyrazine hydrochloride (1-4)

Scheme 1



Step A: Preparation of bishydrazide (1-1)

Hydrazine (20.1 g, 35 wt% in water, 0.22 mol) was mixed with 310 mL of acetonitrile. 31.5 g of ethyl trifluoroacetate (0.22 mol) was added over 60 min. The internal temperature was increased to 25° C. from 14° C. The resulting solution was aged at 22-25° C. for 60 min. The was cooled to 7° C. 17.9 g of 50 wt % aqueous NaOH (0.22 mol) and 25.3 g of chloroacetyl chloride (0.22 mol) were added simultaneously over 130 min at a temperature below 16° C. When the reaction was complete, the mixture was vacuum distilled to

remove water and ethanol at 27~30° C. and under 26 ~27 in Hg vacuum. During the distillation, 720 mL of acetonitrile was added slowly to maintain constant volume (approximately 500 mL). The slurry was filtered to remove sodium chloride. The cake was rinsed with about 100 mL of acetonitrile. Removal of the solvent afforded bis-hydrazide 1-1 (43.2 g, 96.5% yield, 94.4 area % pure by HPLC assay).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.2 (s, 2H), 10.7 (s, 1H), and 11.6 (s, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-d_6): δ 41.0, 116.1 (q, J=362 Hz), 155.8 (q, J=50 Hz), and 165.4 ppm.

Step B: Preparation of 5-(trifluoromethyl)-2-(chloromethyl)-1.3.4-oxadiazole (1-2)

Bishydrazide 1-1 from Step A (43.2 g, 0.21 mol) in ACN (82 mL) was cooled to 5° C. Phosphorus oxychloride (32.2 g, 0.21 mol) was added, maintaining the temperature below 10° C. The mixture was heated to 80° C. and aged at this temperature for 24 h until HPLC showed less than 2 area % of 1-1. In a separate vessel, 260 mL of IPAc and 250 mL of water were mixed and cooled to 0° C. The reaction slurry was charged to the quench keeping the internal temperature below 10° C. After the addition, the mixture was agitated vigorously for 30 min, the temperature was increased to room temperature and the aqueous layer was cut. The organic layer was then washed with 215 mL of water, 215 mL of 5 wt % aqueous sodium bicarbonate and finally 215 mL of 20 wt % aqueous brine solution. HPLC assay yield after work up was 86-92%. Volatiles were removed by distillation at 75-80 mm Hg, 55° C. to afford an oil which could be used directly in Step C without further purification. Otherwise the product can be purified by distillation to afford 1-2 in 70-80% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.8 (s, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.1, 115.8 (q, J=337 Hz), 156.2 (q, J=50 Hz), and 164.4 ppm.

Step C: Preparation of N-[(2Z)-piperazin-2-ylidene]trifluoroacetohydrazide (1-3)

To a solution of ethylenediamine (33.1 g, 0.55 mol) in methanol (150 mL) cooled at −20° C. was added distilled oxadiazole 1-2 from Step B (29.8 g, 0.16 mol) while keeping the internal temperature at −20° C. After the addition was complete, the resulting slurry was aged at −20° C. for 1 h. Ethanol (225 mL) was then charged and the slurry slowly warmed to −5° C. After 60 min at −5° C., the slurry was filtered and washed with ethanol (60 mL) at −5° C. Amidine 1-3 was obtained as a white solid in 72% yield (24.4 g, 99.5 area wt % pure by HPLC).

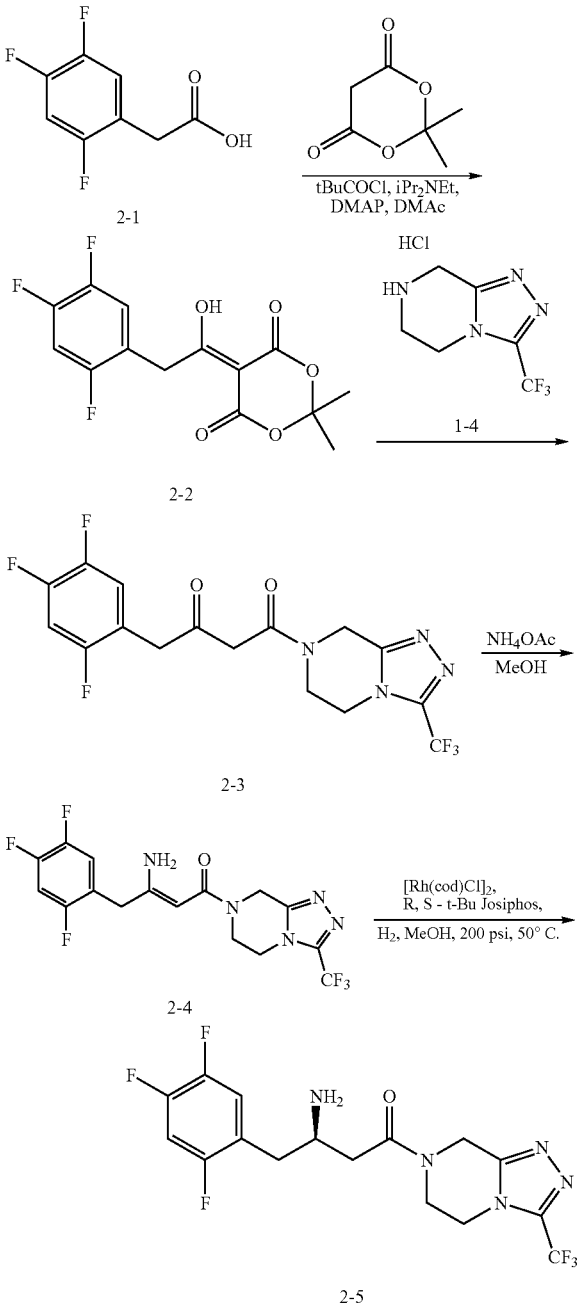
^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.9 (t, 2H), 3.2 (t, 2H), 3.6 (s, 2H), and 8.3 (b, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-d_6): δ 40.8, 42.0,43.3, 119.3 (q, J=350 Hz), 154.2, and 156.2 (q, J=38 Hz) ppm.

Step D: Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4.3-a]pyrazine hydrochloride (1-4)

A suspension of amidine 1-3 (27.3 g, 0.13 mol) in 110 mL of methanol was warmed to 55° C. 37% Hydrochloric acid (11.2 mL, 0.14 mol) was added over 15 min at this temperature. During the addition, all solids dissolved resulting in a clear solution. The reaction was aged for 30 min. The solution was cooled down to 20° C. and aged at this temperature until a seed bed formed (10 min to 1 h). 300 mL of MTBE was charged at 20° C. over 1 h. The resulting slurry was cooled to 2° C., aged for 30 min and filtered. Solids were washed with 50 mL of ethanol:MTBE (1:3) and dried under vacuum at 45° C. Yield of triazole 1-4 was 26.7 g (99.5 area wt % pure by HPLC).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.6 (t, 2H), 4.4 (t, 2H), 4.6 (s, 2H), and 10.6 (b, 2H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ: 39.4, 39.6, 41.0, 118.6 (q, J=325 Hz), 142.9 (q, J=50 Hz), and 148.8 ppm.

Scheme 2



Step A: Preparation of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-one (2-3)

2,4,5-Trifluorophenylacetic acid (2-1 (150 g, 0.789 mol), Meldrum's acid (125 g, 0.868 mol), and 4-(dimethylamino) pyridine (DMAP) (7.7 g, 0063 mol) were charged into a 5 L three-neck flask. N,N-Dimethylacetamide (DMAc) (525 mL) was added in one portion at room temperature to

dissolve the solids. N,N-diisopropylethylamine (282 mL, 1.62 mol) was added in one portion at room temperature while maintaining the temperature below 40° C. Pivaloyl chloride (107 mL, 0.868 mol) was added dropwise over 1 to 2 h while maintaining the temperature between 0 and 5° C. The reaction mixture was aged at 5° C. for 1 h. Triazole hydrochloride 14 (180 g, 0.789 mol) was added in one portion at 40-50° C. The reaction solution was aged at 70° C. for several h. 5% Aqueous sodium hydrogencarbonate solution (625 mL) was then added dropwise at 20-45° C. The batch was seeded and aged at 20-30° C. for 1-2 h. Then an additional 525 mL of 5% aqueous sodium hydrogencarbonate solution was added dropwise over 2-3 h. After aging several h at room temperature, the slurry was cooled to 0-5° C. and aged 1 h before filtering the solid. The wet cake was displacement-washed with 20% aqueous DMAc (300 mL), followed by an additional two batches of 20% aqueous DMAc (400 mL), and finally water (400 mL). The cake was suction-dried at room temperature. The isolated yield of final product 2-3 was 89%.

Step B: Preparation of (2Z)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl-]-1-(2,4,5-trifluorophenyl)but-2-en-2-amine (2-4)

A 5 L round-bottom flask was charged with methanol (100 mL), the ketoamide 2-3 (200 g), and ammonium acetate (110.4 g). Methanol (180 mL) and 28% aqueous ammonium hydroxide (58.6 mL) were then added keeping the temperature below 30° C. during the addition. Additional methanol (100 mL) was added to the reaction mixture. The mixture was heated at reflux temperature and aged for 2 h. The reaction was cooled to room temperature and then to about 5° C. in an ice-bath. After 30 min, the solid was filtered and dried to afford 2-4 as a solid (180 g); m.p. 271.2° C.

Step C: Preparation of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1 2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine (2-5)

Into a 500 ml flask were charged chloro(1,5-cyclooctadiene)rhodium(I) dimer $\{[Rh(cod)Cl]_2\}$(292 mg, 1.18 mmol) and (R,S) t-butyl Josiphos (708 mg, 1.3 mmol) under a nitrogen atmosphere. Degassed MeOH was then added (200 mL) and the mixture was stirred at room temperature for 1 h. Into a 4 L hydrogenator was charged the enamine amide 2-4 (118 g, 0.29 mol) along with MeOH (1 L). The slurry was degassed. The catalyst solution was then transferred to the hydrogenator under nitrogen. After degassing three times, the enamine amide was hydrogenated under 200 psi hydrogen gas at 50° C. for 13 h. Assay yield was determined by HPLC to be 93% and optical purity to be 94% ee.

The optical purity was further enhanced in the following manner. The methanol solution from the hydrogenation reaction (18 g in 180 mL MeOH) was concentrated and switched to methyl t-butyl ether (MTBE) (45 mL). Into this solution was added aqueous H_3PO_4 solution (0.5 M, 95 mL). After separation of the layers, 3N NaOH (35 mL) was added to the water layer, which was then extracted with MTBE (180 mL+100 mL). The MTBE solution was concentrated and solvent switched to hot toluene (180 mL, about 75° C.). The hot toluene solution was then allowed to cool to 0° C. slowly (5-10 h). The crystals were isolated by filtration (13 g, yield 72%, 98-99% ee); m.p. 114.1-115.7° C.

^{1}H NMR (300 MHz, CD_3CN): δ 7.26 (m), 7.08 (m), 4.90 (s), 4.89 (s), 4.14 (m), 3.95 (m), 3.40 (m), 2.68 (m), 2.49 (m), 1.40 (bs).

Compound 2-5 exists as amide bond rotamers. Unless indicated, the major and minor rotamers are grouped together since the carbon-13 signals are not well resolved:

^{13}C NMR (CD_3CN): δ 171.8, 157.4 (ddd , J_{CF}=242.4, 9.2, 2.5 Hz), 152.2 (major), 151.8 (minor), 149.3 (ddd; J_{CF}=246.7, 14.2, 12.9 Hz), 147.4 (ddd, J_{CF}=241.2, 12.3, 3.7 Hz), 144.2 (q, J_{CF}=38.8 Hz), 124.6 (ddd, J_{CF}=18.5, 5.9, 4.0 Hz), 120.4 (dd, J_{CF}=19.1, 6.2 Hz), 119.8 (q, J_{CF}=268.9 Hz), 106.2(dd, J_{CF}=29.5, 20.9 Hz), 50.1, 44.8, 44.3 (minor), 43.2 (minor), 42.4, 41.6 (minor), 41.4, 39.6, 38.5 (minor), 36.9.

The crystalline free base can also be isolated as follows:

(a) The reaction mixture upon completion of the hydrogenation step is charged with 25 wt % of Ecosorb C-941. The mixture is stirred under nitrogen for one h and then filtered. The cake is washed with 2 L/kg of methanol. Recovery of free base is about 95% and optical purity about 95% ee.

(b) The freebase solution in methanol is concentrated to 3.5-4.0 L/kg volume (based on free base charge) and then solvent-switched into isopropanol (IPA) to final volume of 3.0 L/kg IPA.

(c) The slurry is heated to 40° C. and aged 1 h at 40° C. and then cooled to 25° C. over 2 h.

(d) Heptane (7 L/kg) is charged over 7 h and the slurry stirred for 12 h at 22-25° C. The supernatant concentration before filtering is 10-12 mg/g.

(e) The slurry is filtered and the solid washed with 30% IPA/heptane (2 L/kg).

(f) The solid is dried in a vacuum oven at 40° C.

(g) The optical purity of the free base is about 99% ee.

The following high-performance liquid chromatographic (HPLC) conditions were used to determine percent conversion to product:

Column: Waters Symmetry C18, 250 mm×4.6 mm
Eluent: Solvent A: 0.1 vol % $HClO_4/H_2O$
Solvent B: acetonitrile
Gradient: 0 min 75% A: 25% B
10 min 25% A: 75% B
12.5 min 25% A: 75% B
15 min 75% A: 25% B
Flow rate: 1 mL/min
Injection Vol.: 10 μL
UV detection: 210 nm
Column temp.: 40° C.
Retention times: compound 2-4: 9.1 min
compound 2-5: 5.4 min
tBu Josiphos: 8.7 min

The following high-performance liquid chromatographic (HPLC) conditions were used to determine optical purity:

Column: Chirapak, AD-H, 250 mm×4.6 mm
Eluent: Solvent A: 0.2 vol. % diethylamine in heptane
Solvent B: 0.1 vol % diethylamine in ethanol
Isochratic Run Time: 18 min
Flow rate: 0.7 mL/min
Injection Vol.: 7 μL
UV detection: 268 nm
Column temp.: 35° C.
Retention times: (R)-amine 2-5: 13.8 min
(S)-amine 2-5: 11.2 min

(2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,24]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine dihydrogenphosphate monohydrate

A 250 mL round bottom flask equipped with an overhead stirrer, heating mantle and thermocouple, was charged with 31.5 mL of isopropanol (IPA), 13.5 mL water, 15.0 g (36.9 mmol) of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,

2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine freebase and 4.25 g (36.9 mmol) of 85% aqueous phosphoric acid. The mixture was heated to 75° C. A thick white precipitate formed at lower temperatures but dissolved upon reaching 75° C. The solution was cooled to 68° C. and then held at that temperature for 2 h. A slurry bed of solids formed during this age time [the solution can be seeded with 0.5 to 5 wt % of small particle size (alpine milled) monohydrate]. The slurry was then cooled at a rate of 4° C./h to 21° C. and then held overnight. 105 mL of EPA was then added to the slurry. After 1 h the slurry was filtered and washed with 45 mL IPA (solids can also be washed with a water/IPA solution to avoid turnover to other crystal forms). The solids were dried on the frit with open to air. 18.6 g of solids were recovered. The solids were found to be greater than 99.8% pure by HPLC area percentage (HPLC conditions same as those given above). The particle size distribution analysis of the isolated solids showed a mean PSD of 80 microns with 95% less than 180 microns. The crystal form of the solids was shown to be monohydrate by X-ray powder diffraction and thermogravimetric analysis.

X-ray powder diffraction studies are widely used to characterize molecular structures, crystallinity, and polymorphism. The X-ray powder diffraction pattern of the crystalline dihydrogenphosphate monohydrate was generated on a Philips Analytical X'Pert PRO X-ray Diffraction System with PW3040/60 console. A PW3373/00 ceramic Cu LEF X-ray tube K-Alpha radiation was used as the source.

FIG. **1** shows the X-ray diffraction pattern for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. The monohydrate exhibited characteristic diffraction peaks corresponding to d-spacings of 7.42, 5.48, and 3.96 angstroms. The monohydrate was further characterized by the d-spacings of 6.30, 4.75, and 4.48 angstroms. The monohydrate was even further characterized by the d-spacings of 5.85, 5.21, and 3.52 angstroms.

In addition to the X-ray powder diffraction patterns described above, the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II was further characterized by its solid-state carbon-13 and fluorine-19 nuclear magnetic resonance (NMR) spectra. The solid-state carbon-13 NMR spectrum was obtained on a Bruker DSX 400WB NMR system using a Bruker 4 mm double resonance CPMAS probe. The carbon-13 NMR spectrum utilized proton/carbon-13 cross-polarization magic-angle spinning with variable-amplitude cross polarization. The sample was spun at 15.0 kHz, and a total of 2048 scans were collected with a recycle delay of 20 seconds. A line broadening of 40 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported on the TMS scale using the carbonyl carbon of glycine (176.03 p.p.m.) as a secondary reference.

The solid-state fluorine-19 NMR spectrum was obtained on a Bruker DSX 400WB NMR system using a Bruker 4 mm CRAMPS probe. The NMR spectrum utilized a simple pulse-acquire pulse program. The samples were spun at 15.0 kHz, and a total of 16 scans were collected with a recycle delay of 30 seconds. A vespel endcap was utilized to minimize fluorine background. A line broadening of 100 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported using poly(tetrafluoroethylene) (teflon) as an external secondary reference which was assigned a chemical shift of −122 ppm.

FIG. **2** shows the solid-state carbon-13 CPMAS NMR spectrum for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. The monohydrate form exhibited characteristic signals with chemical shift values of 169.1, 120.8, and 46.5 p.p.m. Further characteristic of the monohydrate form were the signals with chemical shift values of 159.0, and 150.9, and 40.7 ppm.

FIG. **3** shows the solid-state fluorine-19 MAS NM spectrum for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. The monohydrate form exhibited characteristic signals with chemical shift values of −64.5, −114.7, −136.3, and −146.2 p.p.m. Further characteristic of the monohydrate form were the signals with chemical shift values of −96.5, −104.4, −106.3, and −154.5 ppm.

FIG. **4** shows the characteristic thermogravimetric analysis (TGA) curve for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. A Perkin Elmer model TGA 7 or equivalent instrument was used. Experiments were performed under a flow of nitrogen and using a heating rate of 10° C./min to a maximum temperature of approximately 250° C. After automatically taring the balance, 5 to 20 mg of sample was added to the platinum pan, the furnace was raised, and the heating program started. Weight/temperature data were collected automatically by the instrument. Analysis of the results was carried out by selecting the Delta Y function within the instrument software and choosing the temperatures between which the weight loss was to be calculated. Weight losses are reported up to the onset of decomposition/evaporation. TGA indicated a weight loss of about 3.3647 % from ambient temperature to about 250° C.

FIG. **5** shows the characteristic DSC curve for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. A TA Instruments DSC 2910 or equivalent instrumentation was used. Between 2 and 6 mg sample was weighed into an open pan. This pan was then crimped and placed at the sample position in the calorimeter cell. An empty pan was placed at the reference position. The calorimeter cell was closed and a flow of nitrogen was passed through the cell. The heating program was set to heat the sample at a heating rate of 10° C./min to a temperature of approximately 250° C. The heating program was started. When the run was completed, the data were analyzed using the DSC analysis program contained in the system software. The melting endotherm was integrated between baseline temperature points that are above and below the temperature range over which the endotherm was observed. The data reported are the onset temperature, peak temperature, and enthalpy.

The crystalline dihydrogenphosphate salt monohydrate of the present invention has a phase purity of at least about 5% of the form with the above X-ray powder diffraction, fluorine-19 MAS NMR, carbon-13 CPMAS NMR, and DSC physical characteristics. In one embodiment the phase purity is at least about 10% of the form with the above solid-state physical characteristics. In a second embodiment the phase purity is at least about 25% of the form with the above solid-state physical characteristics. In a third embodiment the phase purity is at least about 50% of the form with the above solid-state physical characteristics. In a fourth embodiment the phase purity is at least about 75% of the form with the above solid-state physical characteristics. In a fifth embodiment the phase purity is at least about 90% of the form with the above solid-state physical characteristics. In a sixth embodiment the crystalline dihydrogenphosphate salt monohydrate is the substantially phase pure form with the above solid-state physical characteristics. By the term "phase purity" is meant the solid state purity of the dihydrogenphosphate salt monohydrate with regard to a particu-

lar crystalline or amorphous form of the salt as determined by the solid-state physical methods described in the present application.

The crystalline dihydrogenphosphate salt monohydrate was found to be stable under ambient condition. It was found to convert to dehydrated monohydrate if heated to above 40° C. under very dry nitrogen flow. Dehydrated monohydrate converted back to monohydrate under ambient condition.

EXAMPLES OF PHARMACEUTICAL COMPOSITIONS

1) Direct Compression Process:

The dihydrogenphosphate salt monohydrate was formulated into a tablet by a direct compression process. A 100 mg potency tablet was composed of 128.4 mg of the active ingredient, 127.8 mg microcrystalline cellulose, 127.8 mg of mannitol (or 127.8 mg of dicalcium phosphate), 8 mg of croscarmellose sodium, 8 mg of magnesium stearate and 16 mg of Opadry white (proprietary coating material made by Colorcon, West Point, Pa.). The active ingredient, microcrystalline cellulose, mannitol (or dicalcium phosphate), and croscarmellose were first blended, and the mixture was then lubricated with magnesium stearate and pressed into tablets. The tablets were then film coated with Opadry White.

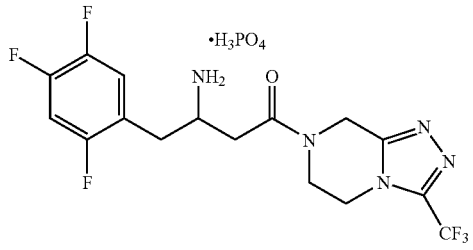
2) Roller Compaction Process:

The dihydrogenphosphate salt monohydrate was formulated into a tablet by a roller compaction process. A 100 mg potency tablet was composed of 128.4 mg of the active ingredient, 45 mg microcrystalline cellulose, 111.6 mg of dicalcium phosphate, 6 mg of croscarmellose sodium, 9 mg of magnesium stearate and 12 mg of Opadry white (proprietary coating material made by Colorcon, West Point, Pa.). The active ingredient, microcrystalline cellulose, dicalcium phosphate, and croscarmellose were first blended, and the mixture was then lubricated with one third the total amount of magnesium stearate and roller compacted into ribbons. These ribbons were then milled and then resulting granules were lubricated with the remaining amount of the magnesium stearate and pressed into tablets. The tablets were then film coated with Opadry White. 3) An intravenous (i.v.) aqueous formulation is defined as the monohydrate of dihydrogenphosphate salt of formula I in 10 mM sodium acetate/0.8% saline solution at pH 4.5±0.2. For a formulation with a concentration of 4.0 mg/mL, 800 mg of NaCl is dissolved in 80 mL of water, then 57.5 μL of glacial acetic acid is added, followed by 512 mg of the dihydrogenphosphate salt monohydrate. The pH is adjusted to 4.5±0.2 with 0.1 N NaOH solution. The final volume is adjusted to 100 mL with water. A 2.0 mg/mL solution can be made by dilution of 50.0 mL of the 4.0 mg/mL solution to 100.0 mL with placebo. A 1.0 mg/mL solution can be made by dilution of 25.0 mL of the 4.0 mg/mL solution to 100.0 mL with placebo.

What is claimed is:

1. A dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I:

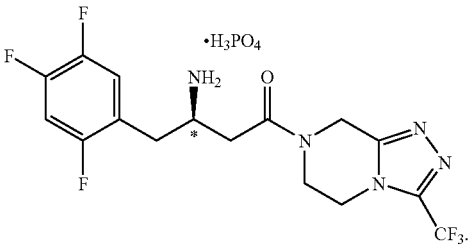
(I)



or a hydrate thereof.

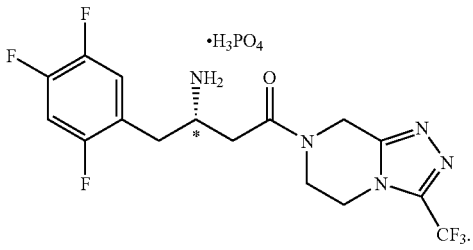
2. The salt of claim **1** of structural formula II having the (R)-configuration at the chiral center marked with an *

(II)



3. The salt of claim **1** of structural formula III having the (S)-configuration at the chiral center marked with an *

(III)



4. The salt of claim **2** characterized in being a crystalline monohydrate.

5. The salt of claim **4** characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 7.42, 5.48, and 3.96 angstroms.

6. The salt of claim **5** further characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 6.30, 4.75, and 4.48 angstroms.

7. The salt of claim **6** further characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 5.85, 5.21, and 3.52 angstroms.

8. The salt of claim **7** further characterized by the X-ray powder diffraction pattern of FIG. **1**.

9. The salt of claim **4** characterized by a solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum showing signals at 169.1, 120.8, and 46.5 ppm.

10. The salt of claim **9** further characterized by a solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum showing signals at 159.0, 150.9, and 40.7 ppm.

11. The salt of claim **10** further characterized by the solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum of FIG. **2**.

12. The salt of claim **4** characterized by a solid-state fluorine-19 MAS nuclear magnetic resonance spectrum showing signals at −64.5, −114.7, −136.3, and −146.2 ppm.

13. The salt of claim **12** further characterized by a solid-state fluorine-19 MAS nuclear magnetic resonance spectrum showing signals at −96.5, −104.4, −106.3, and −154.5 ppm.

14. The salt of claim **13** further characterized by the solid-state fluorine-19 MAS nuclear magnetic resonance spectrum of FIG. **3**.

15. The salt of claim **4** characterized by the thermogravimetric analysis curve of FIG. **4**.

16. The salt of claim **4** characterized by the differential scanning calorimetric curve of FIG. **5**.

17. A pharmaceutical composition comprising a therapeutically effective amount of the salt according to claim **2** in association with one or more pharmaceutically acceptable carriers.

18. A pharmaceutical composition comprising a therapeutically effective amount of the salt according to claim **4** in association with one or more pharmaceutically acceptable carriers.

19. A method for the treatment of type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the salt according to claim **2** or a hydrate thereof.

20. A method for the treatment of type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the salt according to claim **4**.

21. A process for preparing the salt of claim **2** comprising the step of contacting one equivalent of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine in an organic solvent or aqueous organic solvent with about a one equivalent of phosphoric acid at a temperature in the range of about 25-100° C.

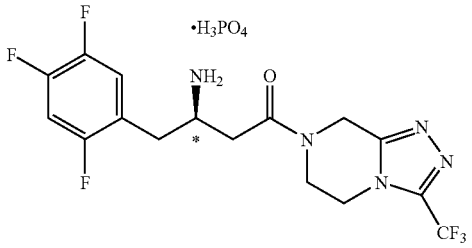
22. The process of claim **21** wherein said organic solvent is a C_1-C_5 linear or branched alkanol.

23. The phosphoric acid salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine prepared according to the process of claim **21**.

24. A process for preparing the crystalline monohydrate of claim **4** comprising the steps of:

(a) crystallizing the dihydrogenphosphate salt of structural formula (II):

(II)



at 25° C. from a mixture of isopropanol and water, such that the water concentration is above 6.8 weight percent;

(b) recovering the resultant solid phase; and

(c) removing the solvent therefrom.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,326,708 B2
APPLICATION NO. : 10/874992
DATED : February 5, 2008
INVENTOR(S) : Cypes et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 884 days.

Signed and Sealed this
Ninth Day of February, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,326,708 B2
APPLICATION NO. : 10/874992
DATED : February 5, 2008
INVENTOR(S) : Stephen Howard Cypes et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

In Column 16, Claim 5, Lines 2-3, replace "absorption bands obtained from the X-ray powder diffraction pattern at spectral" with --diffraction peaks obtained from the X-ray powder diffraction pattern corresponding to--.

In Column 16, Claim 6, Lines 2-3, replace "absorption bands obtained from the X-ray powder diffraction pattern at spectral" with --diffraction peaks obtained from the X-ray powder diffraction pattern corresponding to--.

In Column 16, Claim 7, Lines 2-3, replace "absorption bands obtained from the X-ray powder diffraction pattern at spectral" with --diffraction peaks obtained from the X-ray powder diffraction pattern corresponding to--.

Signed and Sealed this
Ninth Day of February, 2021

Drew Hirshfeld
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

EXHIBIT B

US008414921B2

(12) **United States Patent**
Kamali et al.

(10) **Patent No.: US 8,414,921 B2**
(45) **Date of Patent: Apr. 9, 2013**

(54) **PHARMACEUTICAL COMPOSITIONS OF COMBINATIONS OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS WITH METFORMIN**

(75) Inventors: **Ashkan Kamali**, West Conshohocken, PA (US); **Laman Alani**, Lansdale, PA (US); **Kyle A. Fliszar**, Quakertown, PA (US); **Soumojeet Ghosh**, Lansdale, PA (US); **Monica Tijerina**, Doylestown, PA (US)

(73) Assignee: **Merck Sharp & Dohme Corp.**, Rahway, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(86) PCT No.: **PCT/US2006/047380**

§ 371 (c)(1),
(2), (4) Date: **May 29, 2008**

(87) PCT Pub. No.: **WO2007/078726**

PCT Pub. Date: **Jul. 12, 2007**

(65) **Prior Publication Data**

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Related U.S. Application Data

(60) Provisional application No. 60/750,954, filed on Dec. 16, 2005.

(51) **Int. Cl.**
A61K 9/20 (2006.01)

(52) **U.S. Cl.** **424/465**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are pharmaceutical compositions comprising fixed-dose combinations of a dipeptidyl peptidase-4 inhibitor and metformin, methods of preparing such pharmaceutical compositions, and methods of treating Type 2 diabetes with such pharmaceutical compositions.

28 Claims, No Drawings

PHARMACEUTICAL COMPOSITIONS OF COMBINATIONS OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS WITH METFORMIN

CROSS REFERENCE TO RELATED APPLICATIONS

This application is the National Stage of International Application No. PCT/US2006/047380, filed 12 Dec. 2006, which claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application No. 60/750,954, filed Dec. 16, 2005.

BACKGROUND OF THE INVENTION

Type 2 diabetes is a chronic and progressive disease arising from a complex pathophysiology involving the dual endocrine defects of insulin resistance and impaired insulin secretion. The treatment of Type 2 diabetes typically begins with diet and exercise, followed by oral antidiabetic monotherapy. For many patients, these regimens do not sufficiently control glycaemia during long-term treatment, leading to a requirement for combination therapy within several years following diagnosis. However, co-prescription of two or more oral antidiabetic drugs may result in treatment regimens that are complex and difficult for many patients to follow. Combining two or more oral antidiabetic agents into a single tablet provides a potential means of delivering combination therapy without adding to the complexity of patients' daily regimens. Such formulations have been well accepted in other disease indications, such as hypertension (HYZAAR™ which is a combination of losartan potassium and hydrochlorothiazide) and cholesterol lowering (VYTORIN™ which is a combination of simvastatin and ezetimibe). The selection of effective and well-tolerated treatments is a key step in the design of a combination tablet. Moreover, it is essential that the components have complementary mechanisms of action and compatible pharmacokinetic profiles. Examples of marketed combination tablets containing two oral antidiabetic agents include Glucovance™ (metformin and glyburide), Avandame™ (metformin and rosiglitazone), and Metaglip™ (metformin and glipizide).

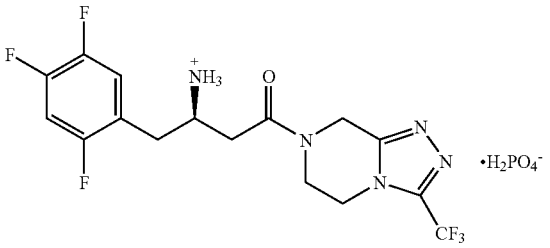
Metformin represents the only oral antidiabetic agent proven to reduce the total burden of microvascular and macrovascular diabetic complications and to prolong the lives of Type 2 diabetic patients. Furthermore, metformin treatment is often associated with reductions in body weight in overweight patients and with improvements in lipid profiles in dyslipidemic patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors represent a novel class of agents that are being developed for the treatment or improvement in glycemic control in patients with Type 2 diabetes. Specific DPP-4 inhibitors currently in clinical trials for the treatment of Type 2 diabetes include sitagliptin phosphate (MK-0431), vildagliptin (LAF-237), saxagliptin (BMS47718), P93/01 (Prosidion), SYR322 (Takeda), GSK 823093, Roche 0730699, TS021 (Taisho), E3024 (Eisai), and PHX-1149 (Phenomix). For example, oral administration of vildagliptin or sitagliptin to human Type 2 diabetics has been found to reduce fasting glucose and postprandial glucose excursion in association with significantly reduced HbA_{1c} levels. For reviews on the application of DPP-4 inhibitors for the treatment of Type 2 diabetes, reference is made to the following publications: (1) H.-U. Demuth, et al., "Type 2 diabetes—Therapy with dipeptidyl peptidase IV inhibitors, *Biochim. Biophys. Acta,* 1751: 33-44 (2005) and (2) K. Augustyns, et al., "Inhibitors of proline-specific dipeptidyl

peptidases: DPP IV inhibitors as a novel approach for the treatment of Type 2 diabetes," *Expert Opin. Ther. Patents,* 15: 1387-1407 (2005).

Sitagliptin phosphate having structural formula I below is the dihydrogenphosphate salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine.

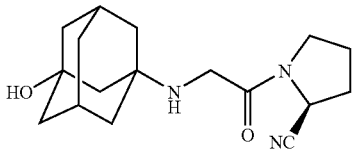
(I)



In one embodiment sitagliptin phosphate is in the form of a crystalline anhydrate or monohydrate. In a class of this embodiment, sitagliptin phosphate is in the form of a crystalline monohydrate. Sitagliptin free base and pharmaceutically acceptable salts thereof are disclosed in U.S. Pat. No. 6,699,871, the contents of which are hereby incorporated by reference in their entirety. Crystalline sitagliptin phosphate monohydrate is disclosed in international patent publication WO 2005/0031335 published on Jan. 13, 2005. For a review on sitagliptin phosphate (MK-0431) including its synthesis and pharmacological properties, reference is made to the following publications: (1) C. F. Deacon, "MK-431," *Curr. Opin. Invest. Drugs,* 6: 419-426 (2005) and (2) "MK-0431", *Drugs of the Future,"* 30: 337-343 (2005).

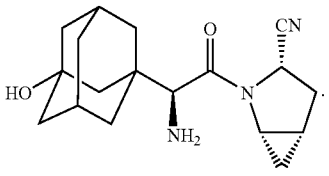
Vildagliptin (LAF-237) is the generic name for (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine having structural formula II. Vildagliptin is specifically disclosed in U.S. Pat. No. 6,166,063, the contents of which are hereby incorporated by reference in their entirety.

(II)



Saxagliptin (BMS-47718) is a methanoprolinenitrile of structural formula III below. Saxagliptin is specifically disclosed in U.S. Pat. No. 6,395,767, the contents of which are hereby incorporated by reference in their entirety.

(III)



The present invention provides for pharmaceutical compositions of a fixed-dose combination of a DPP-4 inhibitor and

metformin which are prepared by dry or wet processing methods. The pharmaceutical compositions of the present invention provide for immediate release of the two active pharmaceutical ingredients. In one embodiment the pharmaceutical compositions of the present invention are in the dosage form of a tablet, and, in particular, a film-coated tablet.

The present invention also provides a process to prepare pharmaceutical compositions of a fixed-dose combination of a DPP-4 inhibitor and metformin by dry or wet processing methods. The dry processing methods include dry compression and dry granulation, and the wet processing methods include wet granulation.

Another aspect of the present invention provides methods for the treatment of Type 2 diabetes by administering to a host in need of such treatment a therapeutically effective amount of a pharmaceutical composition of the present invention.

These and other aspects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention is directed to novel pharmaceutical compositions comprising fixed dose combinations of a DPP-4 inhibitor and metformin, or pharmaceutically acceptable salts of each thereof, methods of preparing such pharmaceutical compositions, and methods of treating Type 2 diabetes with such pharmaceutical compositions. In particular, the invention is directed to pharmaceutical compositions comprising fixed-dose combinations of sitagliptin phosphate and metformin hydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention is directed to dosage forms for the medicinal administration of a fixed-dose combination of a DPP-4 inhibitor and metformin. Such dosage forms may be in the powder or solid format and include tablets, capsules, sachets, etc. A particular solid dosage form relates to tablets comprising a fixed-dose combination of a DPP-4 inhibitor and metformin hydrochloride (1,1-dimethylbiguanide hydrochloride).

In a particular aspect of the present invention, the pharmaceutical compositions comprise (1) a DPP-4 inhibitor, or a pharmaceutically acceptable salt thereof, as one of the two active pharmaceutical ingredients; (2) metformin hydrochloride as the second active pharmaceutical ingredient; and (3) a lubricant or glidant. In an embodiment of this aspect of the present invention, the pharmaceutical compositions may also contain one or more excipients which excipients are selected from the group consisting of one or more binding agents (binders); one or more diluents; one or more surfactants or wetting agents; one or more disintegrants; and one or more antioxidants.

In another embodiment of this aspect of the invention, the DPP-4 inhibitor is selected from the group consisting of sitagliptin, vildagliptin, saxagliptin, P93/01, SYR322, GSK 823093, Roche 0730699, TS021, E3024, and PHX-1149. In a class of this embodiment the DPP-4 inhibitor is sitagliptin, vildagliptin, or saxagliptin. In a subclass of this class, the DPP-4 inhibitor is sitagliptin.

A preferred pharmaceutically acceptable salt of sitagliptin is the dihydrogenphosphate salt of structural formula I above (sitagliptin phosphate). A preferred form of the dihydrogenphosphate salt is the crystalline monohydrate disclosed in WO 2005/0031335.

The preparation of sitagliptin and pharmaceutically acceptable salts thereof is disclosed in U.S. Pat. No. 6,699,871, the contents of which are herein incorporated by reference in their entirety. The preparation of sitagliptin phosphate monohydrate is disclosed in international patent publication WO 2005/0031335 published on Jan. 13, 2005, the contents of which are herein incorporated by reference in their entirety.

The dosage strength of the DPP-4 inhibitor for incorporation into the pharmaceutical compositions of the present invention is an amount from about 1 milligram to about 250 milligrams of the active moiety. A preferred dosage strength of the DPP-4 inhibitor is an amount from about 25 milligrams to about 200 milligrams of the active moiety. Discrete dosage strengths are the equivalent of 25, 50, 75, 100, 150, and 200 milligrams of the DPP-4 inhibitor active moiety. By "active moiety" is meant the free base form of the DPP-4 inhibitor as an anhydrate.

The unit dosage strength of sitagliptin free base anhydrate (active moiety) for inclusion into the fixed-dose combination pharmaceutical compositions of the present invention is 25, 50, 75, 100, 150, or 200 milligrams. A preferred dosage strength of sitagliptin is 50 or 100 milligrams. An equivalent amount of sitagliptin phosphate monohydrate to the sitagliptin free base anhydrate is used in the pharmaceutical compositions, namely, 32.13, 64.25, 96.38, 128.5, 192.75, and 257 milligrams, respectively.

The unit dosage strength of the metformin hydrochloride for incorporation into the fixed-dose combination of the present invention is 250, 500, 625, 750, 850, and 1000 milligrams. These unit dosage strengths of metformin hydrochloride represent the dosage strengths approved in the U.S. for marketing to treat Type 2 diabetes.

Specific embodiments of dosage strengths for sitagliptin and metformin hydrochloride in the fixed-dose combinations of the present invention are the following:

(1) 50 milligrams of sitagliptin (equivalent to 64.25 milligrams of sitagliptin phosphate monohydrate) and 500 milligrams metformin hydrochloride;

(2) 50 milligrams of sitagliptin (equivalent to 64.25 milligrams of sitagliptin phosphate monohydrate) and 850 milligrams metformin hydrochloride;

(3) 50 milligrams of sitagliptin (equivalent to 64.25 milligrams of sitagliptin phosphate monohydrate) and 1000 milligrams metformin hydrochloride;

(4) 100 milligrams of sitagliptin (equivalent to 128.5 milligrams of sitagliptin phosphate monohydrate) and 500 milligrams metformin hydrochloride;

(5) 100 milligrams of sitagliptin (equivalent to 128.5 milligrams of sitagliptin phosphate monohydrate) and 850 milligrams metformin hydrochloride; and

(6) 100 milligrams of sitagliptin (equivalent to 128.5 milligrams of sitagliptin phosphate monohydrate) and 1000 milligrams metformin hydrochloride.

The pharmaceutical compositions of the present invention are prepared by wet or dry processing methods. In one embodiment the pharmaceutical compositions are prepared by wet processing methods. In a class of this embodiment the pharmaceutical compositions are prepared by wet granulation methods. With wet granulation either high-shear granulation or fluid-bed granulation may be used. In one embodiment fluid-bed granulation is employed which has the advantage of affording tablets with higher diametric strength.

In a second embodiment the pharmaceutical compositions are prepared by dry processing methods. In a class of this embodiment the pharmaceutical compositions are prepared by direct compression or dry granulation methods. An embodiment of dry granulation is roller compaction.

The pharmaceutical compositions obtained by the dry or wet processing methods may be compressed into tablets, encapsulated, or metered into sachets.

The pharmaceutical compositions contain one or more lubricants or glidants. Examples of lubricants include magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, hydrogenated castor oil, and mixtures thereof. A preferred lubricant is magnesium stearate or sodium stearyl fumarate or a mixture thereof. Examples of glidants include colloidal silicon dioxide, calcium phosphate tribasic, magnesium silicate, and talc.

The pharmaceutical compositions of the present invention optionally contain one or more binding agents. Embodiments of binding agents include hydroxypropylcellulose (HPC), hydroxypropylmethyl cellulose (HMPC), hydroxyethyl cellulose, starch 1500, polyvinylpyrrolidone (povidone), and co-povidone. A preferred binding agent is polyvinylpyrrolidone.

The pharmaceutical compositions of the present invention may also optionally contain one or more diluents. Examples of diluents include mannitol, sorbitol, dibasic calcium phosphate dihydrate, microcrystalline cellulose, and powdered cellulose. A preferred diluent is microcrystalline cellulose. Microcrystalline cellulose is available from several suppliers and includes Avicel PH 101, Avicel PH 102, Avicel, PH 103, Avicel PH 105, and Avicel PH 200, manufactured by the FMC Corporation.

The pharmaceutical compositions of the present invention may also optionally contain a disintegrant. The disintegrant may be one of several modified starches, modified cellulose polymers, or polycarboxylic acids, such as croscarmellose sodium, sodium starch glycollate, polacrilin potassium, and carboxymethylcellulose calcium (CMC Calcium). In one embodiment, the disintegrant is croscarmellose sodium. Croscarmellose sodium NF Type A is commercially available under the trade name "Ac-di-sol."

The pharmaceutical compositions of the present invention may also optionally contain one or more surfactants or wetting agents. The surfactant may be anionic, cationic, or neutral. Anionic surfactants include sodium lauryl sulfate, sodium dodecanesulfonate, sodium oleyl sulfate, and sodium laurate mixed with stearates and talc. Cationic surfactants include benzalkonium chlorides and alkyltrimethylammonium bromides. Neutral surfactants include glyceryl monooleate, polyoxyethylene sorbitan fatty acid esters, polyvinyl alcohol, and sorbitan esters. Embodiments of wetting agents include poloxamer, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, and polyoxyethylene stearates.

An anti-oxidant may optionally be added to the formulation to impart chemical stability. The anti-oxidant is selected from the group consisting of α-tocopherol, γ-tocopherol, δ-tocopherol, extracts of natural origin rich in tocopherol, L-ascorbic acid and its sodium or calcium salts, ascorbyl palmitate, propyl gallate, octyl gallate, dodecyl gallate, butylated hydroxytoluene (BHT), and butylated hydroxyanisole (BHA). In one embodiment, the antioxidant is BHT or BHA.

Preferred dosage forms for the pharmaceutical compositions of the present invention are tablets which are prepared by compression methods. Such tablets may be film-coated such as with a mixture of hydroxypropylcellulose and hydroxypropylmethylcellulose containing titanium dioxide and/or other coloring agents, such as iron oxides, dyes, and lakes; a mixture of polyvinyl alcohol (PVA) and polyethylene glycol (PEG) containing titanium dioxide and/or other coloring agents, such as iron oxides, dyes, and lakes; or any other suitable immediate-release film-coating agent(s). The coat provides taste masking and additional stability to the final tablet. A commercial film-coat is Opadry® which is a formulated powder blend provided by Colorcon.

Finally, a sweetening agent and/or flavoring agent may be added if desired.

In one embodiment of the present invention, the pharmaceutical compositions contain about 3 to 20% by weight of a DPP-4 inhibitor as one of the two pharmaceutically active ingredients; about 25 to 94% by weight of metformin hydrochloride as the second pharmaceutically active ingredient; about 0 to 35% by weight of a binding agent; and about 0.1 to 10% by weight of a lubricant. In a class of this embodiment the binding agent is polyvinylpyrrolidone or hydroxypropylcellulose, and the lubricant is magnesium stearate or sodium stearyl fumarate. In a subclass of this class, the binding agent is polyvinylpyrrolidone, and the lubricant is sodium stearyl fumarate. In another class the pharmaceutical compositions optionally contain about 0 to 3% by weight of a surfactant and/or about 0 to 70% by weight of a diluent. In a subclass of this class, the surfactant is sodium lauryl sulfate and the diluent is microcrystalline cellulose.

In a second embodiment the pharmaceutical compositions of the present invention are prepared by wet granulation methods and comprise about 5 to 18% by weight of a DPP-4 inhibitor as one of the two pharmaceutically active ingredients; about 65 to 77% by weight of metformin hydrochloride as the second pharmaceutically active ingredient; about 4 to 9% by weight of a binding agent; and about 1 to 2% by weight of a lubricant. In a class of this embodiment the binding agent is polyvinylpyrrolidone or hydroxypropylcellulose, and the lubricant is magnesium stearate or sodium stearyl fumarate. In a subclass of this class, the binding agent is polyvinylpyrrolidone. In another class the pharmaceutical compositions optionally contain about 0.5 to 1% to by weight of a surfactant and/or about 5 to 15% by weight of a diluent. In a subclass of this class, the surfactant is sodium lauryl sulfate and the diluent is microcrystalline cellulose.

In a further embodiment of the present invention, the pharmaceutical compositions as envisioned for commercial development are as follows:

Tablets of 50 mg DPP-4 Inhibitor/500 mg Metformin HCl Potency:

About 9% by weight of the DPP-4 inhibitor; about 73% by weight of metformin hydrochloride; about 7% by weight of a binding agent; about 1 to 2% by weight of a lubricant; and optionally about 10% by weight of a diluent and/or about 0.5% by weight of a surfactant. In a class of this embodiment the DPP-4 inhibitor is sitagliptin, vildagliptin, or saxagliptin; the binding agent is polyvinylpyrrolidone, the lubricant is magnesium stearate or sodium stearyl fumarate, the diluent is microcrystalline cellulose, and the surfactant is sodium lauryl sulfate. In a subclass of this class, the DPP-4 inhibitor is sitagliptin.

Tablets of 50 mg DPP-4 Inhibitor/850 mg Metformin HCl Potency:

About 6% by weight of the DPP-4 inhibitor; about 76% by weight of metformin hydrochloride; about 7% by weight of a binding agent; about 1 to 2% by weight of a lubricant; and optionally about 10% by weight of a diluent and/or about 0.5% by weight of a surfactant. In a class of this embodiment the DPP-4 inhibitor is sitagliptin, vildagliptin, or saxagliptin; the binding agent is polyvinylpyrrolidone, the lubricant is magnesium stearate or sodium stearyl fumarate, the diluent is microcrystalline cellulose, and the surfactant is sodium lauryl sulfate. In a subclass the DPP-4 inhibitor is sitagliptin.

Tablets of 50 mg DPP-4 Inhibitor/1000 mg Metformin HCl Potency:

About 5% by weight of the DPP-4 inhibitor; about 77% by weight of metformin hydrochloride; about 7% by weight of a binding agent; about 1 to 2% by weight of a lubricant; and optionally about 10% by weight of a diluent and/or about 0.5% by weight of a surfactant. In a class of this embodiment the DPP-4 inhibitor is sitagliptin, vildagliptin, or saxagliptin; the binding agent is polyvinylpyrrolidone, the lubricant is magnesium stearate or sodium stearyl fumarate, the diluent is microcrystalline cellulose, and the surfactant is sodium lauryl sulfate. In a subclass the DPP-4 inhibitor is sitagliptin.

Tablets of 100 mg DPP-4 Inhibitor/500 mg Metformin HCl Potency:

About 17% by weight of the DPP-4 inhibitor; about 65% by weight of metformin hydrochloride; about 7% by weight of a binding agent; about 1 to 2% by weight of a lubricant; and optionally about 9% by weight of a diluent and/or about 0.5% by weight of a surfactant. In a class of this embodiment the DPP-4 inhibitor is sitagliptin, vildagliptin, or saxagliptin; the binding agent is polyvinylpyrrolidone, the lubricant is magnesium stearate or sodium stearyl fumarate, the diluent is microcrystalline cellulose, and the surfactant is sodium lauryl sulfate. In a subclass the DPP-4 inhibitor is sitagliptin.

Tablets of 100 mg DPP-4 Inhibitor/850 mg Metformin HCl Potency:

About 11% by weight of the DPP-4 inhibitor; about 75% by weight of metformin hydrochloride; about 7% by weight of a binding agent; about 1 to 2% by weight of a lubricant; and optionally about 4% by weight of a diluent and/or about 0.5% by weight of a surfactant. In a class of this embodiment the DPP-4 inhibitor is sitagliptin, vildagliptin, or saxagliptin; the binding agent is polyvinylpyrrolidone, the lubricant is magnesium stearate or sodium stearyl fumarate, the diluent is microcrystalline cellulose, and the surfactant is sodium lauryl sulfate. In a subclass the DPP-4 inhibitor is sitagliptin.

Tablets of 100 mg DPP-4 Inhibitor/1000 mg Metformin HCl Potency:

About 10% by weight of the DPP-4 inhibitor; about 77% by weight of metformin hydrochloride; about 7% by weight of a binding agent; about 1 to 2% by weight of a lubricant; and optionally about 4% by weight of a diluent and/or about 0.5% by weight of a surfactant. In a class of this embodiment the DPP-4 inhibitor is sitagliptin, vildagliptin, or saxagliptin; the binding agent is polyvinylpyrrolidone, the lubricant is magnesium stearate or sodium stearyl fumarate, the diluent is microcrystalline cellulose, and the surfactant is sodium lauryl sulfate. In a subclass the DPP-4 inhibitor is sitagliptin.

The pharmaceutical tablet compositions of the present invention may also contain one or more additional formulation ingredients selected from a wide variety of excipients known in the pharmaceutical formulation art. According to the desired properties of the pharmaceutical composition, any number of ingredients may be selected, alone or in combination, based upon their known uses in preparing tablet compositions. Such ingredients include, but are not limited to, diluents, compression aids, glidants, disintegrants, lubricants, flavors, flavor enhancers, sweeteners, and preservatives.

The term "tablet" as used herein is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes, whether coated or uncoated. Substances which may be used for coating include hydroxypropylcellulose, hydroxypropylmethylcellulose, titanium dioxide, talc, sweeteners, colorants, and flavoring agents.

In one embodiment the pharmaceutical compositions of the present invention are prepared by wet granulation (high shear and/or fluid bed). Granulation is a process in which binding agent is added either through the granulating solution or through addition to the granulating bowl to form granules. The steps involved in the wet granulation method comprise the following:

(1) the active pharmaceutical ingredients metformin hydrochloride and the DPP-4 inhibitor are added to the granulating bowl;

(2) optional disintegrants are added to step 1;

(3) for high shear granulation, the binding agent (such as polyvinylpyrrolidone or hydroxypropylcellulose) is added dry to the granulating bowl and dry mixed for a short period followed by the addition of water with or without a surfactant (such as sodium lauryl sulfate). For fluid bed granulation, both active pharmaceutical ingredients are added to the granulator bowl and the granulating solution comprised of binding agent with or without surfactant in water is added upon fluidization;

(4) granules prepared by high shear granulation are tray-dried in an oven or dried in a fluid bed dryer. For granules prepared by fluid bed granulation, granules are dried in a fluid bed dryer;

(5) dried granules are resized in suitable mill;

(6) optional diluents (such as microcrystalline cellulose and dibasic calcium phosphate dihydrate) are blended with dried granules in a suitable blender;

(7) lubricants or glidants (such as magnesium stearate and sodium stearyl fumarate) are added to the blend from step 6 in a suitable blender;

(8) lubricated granule mixture from step 7 may be filled into bottles, sachets, or capsules or compressed into desired tablet image;

(9) and if desired, the resulting tablets may be film-coated.

The steps involved in the dry processing (direct compression or dry granulation) methods comprise:

(1) the active pharmaceutical ingredients metformin hydrochloride and the DPP-4 inhibitor are added to a suitable blender;

(2) optional disintegrants are added to step 1;

(3) optional binders and/or diluents are added to step 2;

(4) lubricants or glidants are added to step 3;

(5) mixture from step 4 may be filled into bottles, sachets, or capsules or compressed into desired tablet image, or processed through a roller compactor;

(6) if processed through a roller compaction, granules may be resized in a suitable mill, if necessary;

(7) optional diluents may be added to the resulting granules, in a suitable blender to improve compaction properties;

(8) optional lubricants or glidants are added to the blend from step 7;

(9) lubricated granule mixture from step 8 may be filled into bottles, sachets, or capsules or compressed into desired tablet image;

(10) and if desired, the resulting tablets from step 5 or step 9 may be film-coated.

The present invention also provides methods for treating Type 2 diabetes by orally administering to a host in need of such treatment a therapeutically effective amount of one of the fixed-dose combination pharmaceutical compositions of the present invention. In one embodiment the host in need of such treatment is a human. In another embodiment the pharmaceutical composition is in the dosage form of a tablet. The pharmaceutical compositions comprising the fixed-dose combination may be administered once-daily (QD), twice-daily (BID), or thrice-daily (TID).

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not intended to be construed as limitations of the present

invention as many variations thereof are possible without departing from the spirit and scope of the invention.

EXAMPLE 1

Fixed-Dose Combination of 50 Milligrams Sitagliptin and 500 Milligrams Metformin Hydrochloride/Per Tablet—Wet Granulation

Sitagliptin phosphate monohydrate	64.25	mg*
Metformin hydrochloride	500	mg
Polyvinylpyrrolidone	48.2	mg
Sodium lauryl sulfate (SLS)	3.45	mg
Microcrystalline cellulose (Avicel PH-102)	59.3	mg
Sodium stearyl fumarate	13.8	mg
Purified water for granulation step**	39.8	mg for high shear or 354 mg for fluid bed
Opadry ® II	17.2	mg
Purified water for coating step**	68.9	mg

*Equivalent to 50 mg of sitagliptin free base anhydrate.
**Removed during processing.

Method of Manufacture:

Sitagliptin phosphate monohydrate and metformin hydrochloride were loaded into a high shear granulator or a fluid bed granulator. In the case of high shear granulation, purified water containing sodium lauryl sulfate was added to the APIs, in addition to the polyvinylpyrrolidone binding agent over a period of 3-5 minutes. The wetted mass was either tray dried at 40° C. or dried in a fluid-bed dryer at an inlet temperature of 45-60° C. for 3-6 minutes. In the case of fluid bed granulation, purified water containing polyvinylpyrrolidone and sodium lauryl sulfate was added to APIs over a period of 30-60 minutes. The wetted mass was dried in a fluid-bed dryer at an inlet temperature of 45-60° C. The dried material was then milled using a co-mill to achieve fine granules. After milling, microcrystalline cellulose was added to the granules and blended in a twin shell-blender for 200 revolutions. The lubricant (sodium stearyl fumarate) was then added and blended an additional 100 revolutions. The lubricated mixture was compressed using a rotary tablet press to provide a 689 mg uncoated tablet. The tablets were optionally coated with Opadry® II suspension (polyvinyl alcohol, polyethylene glycol, titanium dioxide, and talc, with or without colorants) to an approximate 2.5% weight gain to provide a 706 mg coated tablet.

EXAMPLE 2

Fixed-Dose Combination of 50 Milligrams Sitagliptin and 850 Milligrams Metformin Hydrochloride/Per Tablet—Wet Granulation

Sitagliptin phosphate monohydrate	64.25	mg*
Metformin hydrochloride	850	mg
Polyvinylpyrrolidone	78.2	mg
Sodium lauryl sulfate (SLS)	5.60	mg
Microcrystalline cellulose (Avicel PH-102)	96.1	mg
Sodium stearyl fumarate	22.3	mg
Purified water for granulation step**	64.9	mg for high shear or 573 mg for fluid bed
Opadry ® II	27.9	mg
Purified water for coating step**	112	mg

*Equivalent to 50 mg of sitagliptin free base anhydrate.
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Method of Manufacture:

Tablets were prepared by wet-granulation using essentially the procedure of Example 1 to provide a 1117 mg uncoated tablet. The tablets were optionally coated with 27.9 mg of a standard Opadry II® film-coat formula to provide a 1145 mg coated tablet.

EXAMPLE 3

Fixed-Dose Combination of 50 Milligrams Sitagliptin and 1000 Milligrams Metformin Hydrochloride/Per Tablet—Wet Granulation

Sitagliptin phosphate monohydrate	64.25	mg*
Metformin hydrochloride	1000	mg
Polyvinylpyrrolidone	91.0	mg
Sodium lauryl sulfate (SLS)	6.50	mg
Microcrystalline cellulose (Avicel PH-102)	112.3	mg
Sodium stearyl fumarate	26	mg
Purified water for granulation step**	75.5	mg for high shear or 667 mg for fluid bed
Opadry ® II	32.5	mg
Purified water for coating step**	130	mg

*Equivalent to 50 mg of sitagliptin free base anhydrate.
**Removed during processing.

Method of Manufacture:

Tablets were prepared by wet-granulation using essentially the procedure of Example 1 to provide a 1300 mg uncoated tablet. The tablets were optionally coated with an Opadry® II suspension (polyvinyl alcohol, polyethylene glycol, titanium dioxide, and talc, with or without colorants) to an approximate 2.5% weight gain to provide a 1333 mg coated tablet.

EXAMPLE 4

Fixed-Dose Combination of 50 Milligrams Sitagliptin and 500 Milligrams Metformin Hydrochloride/Per Tablet—Wet Granulation

Sitagliptin phosphate monohydrate	64.25	mg*
Metformin hydrochloride	500	mg
Polyvinylpyrrolidone	48.2	mg
Microcrystalline cellulose (Avicel PH-102)	69.6	mg
Magnesium stearate	6.89	
Purified water for granulation step**	39.8	mg for high shear or 354 mg for fluid bed
Opadry ® II	17.2	mg
Purified water for coating step**	68.9	mg

*Equivalent to 50 mg of sitagliptin free base anhydrate.
**Removed during processing.

Method of Manufacture:

Sitagliptin phosphate monohydrate and metformin hydrochloride were loaded into a high shear granulator or a fluid bed granulator. In the case of high shear granulation, purified water was added to the APIs, in addition to the polyvinylpyrrolidone binding agent over a period of 3-5 minutes. The wetted mass was either tray dried at 40° C. or dried in a fluid-bed dryer at an inlet temperature of 45-60° C. for 3-6 minutes. In the case of fluid bed granulation, purified water containing polyvinylpyrrolidone was added to APIs over a

period of 30-60 minutes. The wetted mass was dried in a fluid-bed dryer at an inlet temperature of 45-60° C. The dried material was then milled using a co-mill to achieve fine granules. After milling, microcrystalline cellulose was added to the granules and blended in a twin shell-blender for 200 revolutions. The lubricant (magnesium stearate) was then added and blended an additional 100 revolutions. The lubricated mixture was compressed using a rotary tablet press to provide a 689 mg uncoated tablet. The tablet was then optionally film-coated with an Opadry® II suspension (polyvinyl alcohol, polyethylene glycol, titanium dioxide, and talc, with or without colorants) to an approximate 2.5% weight gain to provide a 706 mg coated tablet.

EXAMPLE 5

Fixed-Dose Combination of 50 Milligrams Sitagliptin and 1000 Milligrams Metformin Hydrochloride/Ter Tablet—Wet Granulation

Sitagliptin phosphate monohydrate	64.25	mg*
Metformin hydrochloride	1000	mg
Polyvinylpyrrolidone	91.0	mg
Microcrystalline cellulose (Avicel PH-102)	125.25	mg
Magnesium stearate	13.0	
Sodium lauryl sulfate	6.5	
Purified water for granulation step**	75.5	mg for high shear or 667 mg for fluid bed
Opadry ® II	32.5	mg
Purified water for coating step**	130	mg

*Equivalent to 50 mg of sitagliptin free base anhydrate.

**Removed during processing.

Method of Manufacture:

Sitagliptin phosphate monohydrate and metformin hydrochloride were loaded into a high shear granulator or a fluid bed granulator. In the case of high shear granulation, purified water containing sodium lauryl sulfate was added to the APIs, in addition to the polyvinylpyrrolidone binding agent over a period of 3-5 minutes. The wetted mass was either tray dried at 40° C. or dried in a fluid-bed dryer at an inlet temperature of 45-60° C. for 3-6 minutes. In the case of fluid bed granulation, purified water containing polyvinylpyrrolidone and sodium lauryl sulfate was added to APIs over a period of 30-60 minutes. The wetted mass was dried in a fluid-bed dryer at an inlet temperature of 45-60° C. The dried material was then milled using a co-mill to achieve fine granules. After milling, microcrystalline cellulose was added to the granules and blended in a twin shell-blender for 200 revolutions. The lubricant (magnesium stearate) was then added and blended an additional 100 revolutions. The lubricated mixture was compressed using a rotary tablet press to provide a 1300 mg uncoated tablet. The tablet was then optionally film-coated with an Opadry® II suspension (polyvinyl alcohol, polyethylene glycol, titanium dioxide, and talc, with or without colorants) to an approximate 2.5% weight gain to provide a 1333 mg coated tablet.

EXAMPLE 6

Fixed-Dose Combination of 100 Milligrams Sitagliptin and 1000 Milligrams Metformin Hydrochloride/Per Tablet—Wet Granulation

Sitagliptin phosphate monohydrate	128.5	mg*
Metformin hydrochloride	1000	mg
Polyvinylpyrrolidone	91.0	mg
Sodium lauryl sulfate (SLS)	6.50	mg
Microcrystalline cellulose (Avicel PH-102)	48	mg
Sodium stearyl fumarate	26	mg
Purified water**	667	mg

*Equivalent to 100 mg of sitagliptin free base anhydrate.

**Removed during processing.

Method of Manufacture:

Tablets were prepared by fluid-bed granulation using essentially the procedure of Example 1 to provide a 1300 mg uncoated tablet.

EXAMPLE 7

Fixed-Dose Combination of 100 Milligrams Sitagliptin and 500 Milligrams Metformin Hydrochloride/Per Tablet—Wet Granulation

Sitagliptin phosphate monohydrate	128.5	mg*
Metformin hydrochloride	500	mg
Polyvinylpyrrolidone	53.8	mg
Sodium lauryl sulfate (SLS)	3.84	mg
Microcrystalline cellulose (Avicel PH-102)	66.5	mg
Sodium stearyl fumarate	15.4	mg
Purified water**	394	mg

*Equivalent to 50 mg of sitagliptin free base anhydrate.

**Removed during processing.

Method of Manufacture:

Tablets were prepared by fluid-bed granulation using essentially the procedure of Example 1 to provide a 768 mg uncoated tablet.

What is claimed is:

1. A pharmaceutical composition comprising:

(a) about 3 to 20% by weight of sitagliptin, or a pharmaceutically acceptable salt thereof;

(b) about 25 to 94% by weight of metformin hydrochloride;

(c) about 0.1 to 10% by weight of a lubricant;

(d) about 0 to 35% by weight of a binding agent;

(e) about 0.5 to 1% by weight of a surfactant; and

(f) about 5 to 15% by weight of a diluent.

2. The pharmaceutical composition of claim **1** additionally comprising one or more excipients selected from the group consisting of (a) a disintegrant; (b) a wetting agent; and (c) an anti-oxidant.

3. The pharmaceutical composition of claim **1** comprising:

(a) about 5 to 18% by weight of sitagliptin, or a pharmaceutically acceptable salt thereof;

(b) about 65 to 77% by weight of metformin hydrochloride;

(c) about 1 to 2% by weight of a lubricant;
(d) about 4 to 9% by weight of a binding agent;
(e) about 0.5 to 1% by weight of a surfactant; and
(f) about 5 to 15% by weight of a diluent.

4. The pharmaceutical composition of claim **3** wherein said lubricant is magnesium stearate or sodium stearyl fumarate, and the binding agent is polyvinylpyrrolidone.

5. The pharmaceutical composition of claim **3** comprising:
(a) about 9% by weight of sitagliptin, or a pharmaceutically acceptable salt thereof;
(b) about 73% by weight of metformin hydrochloride;
(c) about 1 to 2% by weight of a lubricant;
(d) about 7% by weight of a binding agent;
(e) about 0.5 to 1% by weight of a surfactant; and
(f) about 5 to 15% by weight of a diluent.

6. The pharmaceutical composition of claim **5** additionally comprising about 0.5% by weight of a surfactant and about 10% by weight of a diluent.

7. The pharmaceutical composition of claim **3** comprising
(a) about 5% by weight of sitagliptin, or a pharmaceutically acceptable salt thereof;
(b) about 77% by weight of metformin hydrochloride;
(c) about 1 to 2% by weight of a lubricant;
(d) about 7% by weight of a binding agent;
(e) about 0.5 to 1% by weight of a surfactant; and
(f) about 5 to 15% by weight of a diluent.

8. The pharmaceutical composition of claim **7** additionally comprising about 0.5% by weight of a surfactant and about 10% by weight of a diluent.

9. The pharmaceutical composition of claim **1** wherein the salt is the dihydrogenphosphate salt.

10. A pharmaceutical composition comprising:
(a) sitagliptin present in a unit dosage strength of 25 to 200 milligrams;
(b) metformin hydrochloride present in a unit dosage strength of 250, 500, 625, 750, 850, or 1000 milligrams;
(c) about 1 to 2% by weight of a lubricant;
(d) about 7% by weight of a binding agent;
(e) about 10% by weight of a diluent; and
(f) about 0.5% by weight of a surfactant.

11. The pharmaceutical composition of claim **10** wherein said lubricant is sodium stearyl fumarate, said binding agent is polyvinylpyrrolidone, said diluent is microcrystalline cellulose, and said surfactant is sodium lauryl sulfate.

12. The pharmaceutical composition of claim **10** wherein sitagliptin is present in a unit dosage strength of 25, 50, 75, 100, 150, or 200 milligrams, and said metformin hydrochloride is present in a unit dosage strength of 500, 850, or 1000 milligrams.

13. The pharmaceutical composition of claim **12** wherein sitagliptin is present in a unit dosage strength of 50 milligrams, and said metformin hydrochloride is present in a unit dosage strength of 500, 850, or 1000 milligrams.

14. The pharmaceutical composition of claim **12** wherein said sitagliptin is present in a unit dosage strength of 50 milligrams, and said metformin hydrochloride is present in a unit dosage strength of 500 or 1000 milligrams.

15. The pharmaceutical composition of claim **1** wherein said composition is in the dosage form of a tablet.

16. A method of treating Type 2 diabetes in a human in need thereof comprising orally administering to said human a pharmaceutical composition of claim **1**.

17. The pharmaceutical composition of claim **1** further comprising one or more agents selected from the group consisting of flavoring agents, colorants, and sweeteners.

18. The pharmaceutical composition of claim **1** prepared by wet granulation methods.

19. The pharmaceutical composition of claim **12** wherein said composition is in the dosage form of a tablet.

20. A method of treating Type 2 diabetes in a human in need thereof comprising orally administering to said human a pharmaceutical composition of claim **12**.

21. A pharmaceutical composition consisting essentially of:
(a) about 3 to 20% by weight of sitagliptin, or a pharmaceutically acceptable salt thereof;
(b) about 25 to 94% by weight of metformin hydrochloride;
(c) about 0.1 to 10% by weight of a lubricant;
(d) about 0 to 35% by weight of a binding agent;
(e) about 0.5 to 1% by weight of a surfactant; and
(f) about 5 to 15% by weight of a diluent.

22. A pharmaceutical composition in the form of a tablet comprising:
a) 64.25 mg[*] of sitagliptin phosphate monohydrate, which is equivalent to 50 mg of sitagliptin free base anhydrate;
b) 500 mg of metformin hydrochloride;
c) 48.2 mg of polyvinylpyrrolidone;
d) 3.45 mg of sodium lauryl sulfate;
e) 59.3 mg of microcrystalline cellulose;
f) 13.8 mg of sodium stearyl fumarate; and
g) 17.2 mg of a film coating.

23. A pharmaceutical composition in the form of a tablet comprising:
a) 64.25 mg[*] of sitagliptin phosphate monohydrate, which is equivalent to 50 mg of sitagliptin free base anhydrate;
b) 850 mg of metformin hydrochloride;
c) 78.2 mg of polyvinylpyrrolidone;
d) 5.60 mg of sodium lauryl sulfate;
e) 96.1 mg of microcrystalline cellulose;
f) 22.3 mg of sodium stearyl fumarate; and
g) 27.9 mg of a film coating.

24. A pharmaceutical composition in the form of a tablet comprising:
a) 64.25 mg[*] of sitagliptin phosphate monohydrate, which is equivalent to 50 mg of sitagliptin free base anhydrate;
b) 1000 mg of metformin hydrochloride;
c) 91.0 mg of polyvinylpyrrolidone;
d) 6.50 mg of sodium lauryl sulfate;
e) 112.3 mg of microcrystalline cellulose;
f) 26 mg of sodium stearyl fumarate; and
g) 32.5 mg of a film coating.

25. A pharmaceutical composition in the form of a tablet comprising:
a) 64.25 mg[*] of sitagliptin phosphate monohydrate, which is equivalent to 50 mg of sitagliptin free base anhydrite;
b) 500 mg of metformin hydrochloride;
c) 48.2 mg of polyvinylpyrrolidone;
d) 69.6 mg of microcrystalline cellulose;
e) 6.89 mg of magnesium stearate; and
f) 17.2 mg of a film coating.

26. A pharmaceutical composition in the form of a tablet comprising:
a) 64.25 mg[*] of sitagliptin phosphate monohydrate, which is equivalent to 50 mg of sitagliptin free base anhydrite;
b) 1000 mg of metformin hydrochloride;
c) 91.0 mg of polyvinylpyrrolidone;
d) 125.25 mg of microcrystalline cellulose;
e) 13.0 mg of magnesium stearate;

f) 6.5 mg of sodium lauryl sulfate; and

g) 32.5 mg of a film coating.

27. A pharmaceutical composition in the form of a tablet comprising:

a) 128.5 mg[*] of sitagliptin phosphate monohydrate, which is equivalent to 100 mg of sitagliptin free base anhydrite;

b) 1000 mg of metformin hydrochloride;

c) 91.0 mg of polyvinylpyrrolidone;

d) 6.50 mg of sodium lauryl sulfate;

e) 48 mg of microcrystalline cellulose; and

f) 26 mg of sodium stearyl fumarate.

28. A pharmaceutical composition in the form of a tablet comprising:

a) 128.5 mg[*] of sitagliptin phosphate monohydrate, which is equivalent to 100 mg of sitagliptin free base anhydrate;

b) 500 mg of metformin hydrochloride;

c) 53.8 mg of polyvinylpyrrolidone;

d) 3.84 mg of sodium lauryl sulfate;

e) 66.5 mg of microcrystalline cellulose; and

f) 15.4 mg of sodium stearyl fumarate.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,414,921 B2
APPLICATION NO. : 12/085722
DATED : April 9, 2013
INVENTOR(S) : Ashkan Kamali et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 587 days.

Signed and Sealed this
Ninth Day of July, 2013

Teresa Stanek Rea
Acting Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,414,921 B2
APPLICATION NO. : 12/085722
DATED : April 9, 2013
INVENTOR(S) : Ashkan Kamali et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

1. Claims 6 & 8 delete “additionally”

2. Claims 22 - 28 - delete “[*]”

3. Claims 25, 26, 27 - replace “anhydrite” with “anhydrate”

Signed and Sealed this
Twenty-first Day of February, 2017

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office